

1 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
2 populations. In fact, Defendants' own reference states that the results from studies where the  
3 patient population is exclusively Japanese cannot be generalized to other populations.<sup>2053</sup> The  
4 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
5 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
7 the Japanese respond differently to lipid lowering agents than Westerners.

8 Further, Defendants have failed to offer a purported combination of references as part of  
9 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
10 motivation to combine Nozaki and Hayashi with the other references of their purported  
11 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
12 references.

13 (iii) Grimsgaard, Mori 2000  
14 and/or Maki Do Not Disclose  
15 Purported Knowledge that  
16 DHA was Responsible for the  
17 Increase in LDL-C

18 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that  
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
20 C levels."<sup>2054</sup> Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*  
21 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
22 rely on to support this statement does not categorize the increase in LDL-C as a "negative effect"  
23 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the

23 <sup>2053</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

24 <sup>2054</sup> Defendants' Joint Invalidity Contentions at 532.

1 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.  
2 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
3 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or  
4 Maki—as in very-high TG patients because patients with higher TG levels had different lipid  
5 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
6 considered fundamentally different from patients with borderline-high or high triglycerides from  
7 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of  
8 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would  
9 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would  
10 substantially increase LDL-C in patients with very high TG levels.

11 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known  
12 that “DHA was responsible for the increase in LDL-C levels.”<sup>2055</sup> The discussion related to  
13 Grimsgaard in Section V.D.3.c.1.a.ii.a.i and Mori 2000 in Section V.D.3.c.1.a.i.a.iii is  
14 incorporated herein by reference.

15 Defendants argue that Maki discloses the administration of purified DHA resulted in the  
16 desired reduction of TGs, but also significantly increased LDL-C levels.<sup>2056</sup> Maki was designed  
17 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with  
18 below-average levels of HDL-C levels.<sup>2057</sup> The DHA supplemented group was administered  
19 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,  
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22 <sup>2055</sup> Defendants’ Joint Invalidity Contentions at 529.

23 <sup>2056</sup> Defendants’ Joint Invalidity Contentions at 532.

24 <sup>2057</sup> Maki at 190.

1 monounsaturated and polyunsaturated fatty acids.<sup>2058</sup> Therefore, Maki demonstrated that when  
2 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average  
3 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is  
4 observed.<sup>2059</sup> However, one cannot attribute the rise in LDL-C solely to DHA, because the  
5 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have  
6 also contributed to the elevation in LDL cholesterol.”<sup>2060</sup> Further, Maki admits that the  
7 “mechanism(s) responsible for the changes in the lipid profile associated with DHA  
8 supplementation are not fully understood.”<sup>2061</sup> Therefore, the results of Maki are inconclusive as  
9 to DHA’s effect alone on LDL-C levels.

10 Defendants mischaracterize the rise in LDL-C associated with the administration of  
11 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-  
12 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in  
13 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol  
14 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of  
15 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level  
16 less worrisome.”<sup>2062</sup> Therefore, when one of ordinary skill in the art reviewed all the lipid effects  
17 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was  
18 “less worrisome” because of the “potentially favorable effects on triglycerides, the  
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20 <sup>2058</sup> Maki at 191.

21 <sup>2059</sup> Maki at 195.

22 <sup>2060</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

23 <sup>2061</sup> Maki at 197.

24 <sup>2062</sup> Maki at 197.

1 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense  
2 particles.”<sup>2063</sup>

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
6 has little effect on LDL-C levels.<sup>2064</sup> Defendants identify no other basis upon which a person of  
7 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,  
8 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

9 (iii) The ‘399 Patent is not Obvious Over the  
10 Omacor PDR/Lovaza PDR, in Combination  
11 with Katayama in View of Satoh and/or in  
View of Satoh or Shinozaki in Further View  
of Contacos

12 With respect to the ‘399 Patent, Defendants present a combination of five references: “the  
13 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering  
14 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in  
15 further view of Contacos.”<sup>2065</sup> Defendants also present charts purporting to assert that an  
16 additional 60 references may be combined in order to render the Claims obvious. Not only do  
17 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate  
18 references, they additionally do not suggest any identify for combining these references.  
19 Although Defendants need not point to an explicit statement in the prior art motivating the  
20 combination of these references, any assertion of an “apparent reason” to combine must find a  
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22 <sup>2063</sup> Maki at 197.

23 <sup>2064</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>2065</sup> Defendants’ Joint Invalidity Contentions at 529.



1 basis in the factual record.<sup>2066</sup> Defendants’ unsupported cobbling of selective disclosures  
2 represents hindsight reconstruction.<sup>2067</sup> Defendants’ contentions are no more than an assertion  
3 that certain claim elements were known in the prior art. Throughout their contentions,  
4 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
5 even the reference as a whole. Each reference, however, must be evaluated for all that it  
6 teaches.<sup>2068</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
9 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty  
10 acid compositions or administration period. The Lovaza PDR further does not disclose a method  
11 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza  
12 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference  
13 would cause a significant increase in LDL-C levels in the very high TG patient population, for  
14 whom the product is indicated. At most, the Lovaza PDR discloses administration of a  
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16 <sup>2066</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2067</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>2068</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an  
2 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG  
3 levels.

4 Defendants formulate an obviousness argument that relies on Contacos.<sup>2069</sup> However,  
5 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim  
6 element, an “apparent reason” or motivation to combine the elements in the manner claimed,<sup>2070</sup>  
7 or “a reasonable expectation of success”<sup>2071</sup> of achieving the claimed invention.

8 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and  
9 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,  
10 Contacos fails to provide motivation to administer purified EPA to a very high TG patient  
11 population and does not provide any reasonable expectation of success in lowering TG levels in  
12 the very high TG patient population without increasing LDL-C. Contacos also fails to provide  
13 motivation to administer purified EPA to a very high TG patient population and does not provide  
14 any reasonable expectation of success in lowering TG levels in the very high TG patient  
15 population without increasing LDL-C.

16 The proposed combinations do not render the independent claim of the ’399 Patent  
17 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
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19 <sup>2069</sup> *Id.*

20 <sup>2070</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 <sup>2071</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

1 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally  
2 and the Lovaza package insert specifically) during prosecution.<sup>2072</sup>

3 The analysis of the independent claim of the '399 Patent is incorporated into all asserted  
4 claims that depend from this Claim.

5 (a) A Person of Ordinary Skill Would  
6 Not Have Been Motivated to  
7 Replace the Mixed Fish Oil Active  
8 Ingredient in Lovaza with EPA of  
9 the Recited Composition

10 For an invention to be obvious, there must have been an “apparent reason” to make it.  
11 The subject matter of the '399 patent claims would not have been obvious in light of these  
12 references because a person of ordinary skill would not have been motivated to purify EPA or  
13 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
14 levels without an increase in LDL-C levels.

15 (i) Katayama, Satoh and/or  
16 Shinozaki Do Not Disclose  
17 Purported Known Clinical  
18 Benefits of Administering  
19 Pure EPA

20 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical  
21 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As  
22 discussed in Section V.D.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely  
23 confirms the safety of long term treatment of Epadel and its ability to lower both serum total  
24 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone  
discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or

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<sup>2072</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).

1 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary  
2 skill view these references as teaching such a benefit for very-high TG patients.

3           Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
4 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
5 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when  
6 compared to baseline, there was no significant effect when compared to placebo.<sup>2073</sup>

7 Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing  
8 LDL-C to be a "clinical benefit" is incorrect.<sup>2074</sup> Satoh does not disclose or suggest that the  
9 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these  
10 references as teaching such a benefit for very-high TG patients. As discussed above, one of  
11 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500  
12 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,  
13 however, would have expected that fish oils (and other TG lowering agents) would substantially  
14 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to  
15 administer purified EPA to a very high TG patient population and does not provide any  
16 reasonable expectation of success in lowering TG levels in the very high TG patient population  
17 without increasing LDL-C.

18           Further, Satoh was a small study conducted in only Japanese patients. This study would  
19 not have been extrapolated to Western populations because the Japanese diet contains much  
20 more fish and has a number of other different attributes. The Japanese consume a higher amount  
21 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference

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23 <sup>2073</sup> Satoh at 145.

24 <sup>2074</sup> Defendants' Joint Invalidation Contentions at 528-29.

1 states that the results from studies where the patient population is exclusively Japanese cannot be  
2 generalized to other populations.<sup>2075</sup> The Japanese diet comprises between 8 and 15 times more  
3 EPA and DHA than typical the typical Western diet. The Western diet typically consists of  
4 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a  
5 person of ordinary skill would understand that the Japanese respond differently to lipid lowering  
6 agents than Westerners.

7 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))  
8 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

9 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without  
10 increasing LDL-C to be a "clinical benefit" is incorrect.<sup>2076</sup> Shinozaki says nothing about an  
11 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by  
12 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."<sup>2077</sup> In  
13 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis  
14 upon which a person of ordinary skill would have sought to combine the composition disclosed  
15 in Shinozaki.

16 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion  
17 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by  
18 Defendants suggest that EPA increases LDL-C.<sup>2078</sup> Defendants identify no other basis upon  
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21 <sup>2075</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
22 other populations.").

23 <sup>2076</sup> Defendants' Joint Invalidation Contentions at 529-29.

24 <sup>2077</sup> Shinozaki at 107-109.

<sup>2078</sup> See, e.g., Rambjor.

1 | which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,  
2 | Satoh, Shinozaki and/or Contacos.

3 | (ii) Geppert and/or Kelley Do  
4 | Not Disclose Purported  
5 | Knowledge that DHA was  
6 | Responsible for the Increase  
7 | in LDL-C

6 | Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
7 | administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
8 | C levels.”<sup>2079</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
9 | known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
10 | rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”  
11 | in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
12 | patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,  
13 | respectively. As discussed above in Section III, a person of ordinary skill would not expect the  
14 | same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or  
15 | Kelley—as in very-high TG patients because patients with higher TG levels had different lipid  
16 | responses compared to patients with lower TG levels. Patients with very-high TG levels were  
17 | considered fundamentally different from patients with borderline-high or high triglycerides from  
18 | a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a  
19 | person of ordinary skill in the art would have expected that fish oils (and other TG lowering  
20 | agents) would not increase LDL-C substantially in patients with normal to borderline high TG

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23 | \_\_\_\_\_  
24 | <sup>2079</sup> Defendants’ Joint Invalidity Contentions at 532.

1 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in  
2 patients with very high TG levels.

3 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA  
4 was responsible for the increase in LDL-C levels.”<sup>2080</sup> Both Geppert and Kelley administer  
5 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.  
6 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the  
7 independent effects of DHA because it is not clear how much of the supplement’s effects can be  
8 attributed to DHA.<sup>2081</sup> For example, Defendants’ own prior art teaches that changes in fatty acid  
9 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.<sup>2082</sup>

10 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to  
11 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been  
12 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior  
13 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”<sup>2083</sup> Rather than reading  
14 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior  
15 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there  
16 was confusion in the art and it was unclear whether DHA increased LDL-C.

17 A person of ordinary skill would have expected that Geppert’s results would be  
18 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA  
19 was the only component of fish oil to increase LDL-C. For example, there is no data comparing  
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<sup>2080</sup> Defendants’ Joint Invalidity Contentions at 530.

22 <sup>2081</sup> See Mori 2006 at 96.

23 <sup>2082</sup> Maki at 197.

24 <sup>2083</sup> Geppert at 784.

1 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying  
2 explain the mechanism of LDL-C increase.<sup>2084</sup> A person of ordinary skill would have not  
3 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

4 Defendants contend that Kelley shows that DHA was responsible for the increase in  
5 LDL-C.<sup>2085</sup> In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day  
6 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible  
7 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon  
8 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate  
9 therapy.<sup>2086</sup> Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in  
10 context with the other lipid effects reported in the study. Kelley states that:

11 DHA supplementation may lower the risk of CVD by reducing  
12 plasma triacylglycerols; triacylglycerol:HDL; the number of  
13 small, dense LDL particles; and mean diameter of VLDL particles.  
14 An increase was observed in fasting LDL cholesterol, but it  
15 is unlikely this increase is detrimental because no increase was  
16 observed in the overall number of LDL particles; actually, there  
17 was an 11% reduction that was statistically not significant. The  
18 reason LDL cholesterol increased despite no change in LDL  
19 particle number was that the LDL particles were made larger and  
20 hence more cholesterol rich by DHA treatment.<sup>2087</sup>

21 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation  
22 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle  
23 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
24 concentrations of atherogenic lipids and lipoproteins and increased concentrations of

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21 <sup>2084</sup> *Id.*

22 <sup>2085</sup> Defendants’ Joint Invalidity Contentions at 530.

23 <sup>2086</sup> Kelley at 329.

24 <sup>2087</sup> Kelley at 329



1 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular  
2 health.”<sup>2088</sup> Rather than concluding that DHA was uniquely responsible for a rise in LDL-C  
3 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely  
4 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with  
5 negative attributes, a person of ordinary skill would understand that the reference taught towards  
6 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400  
7 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the  
8 very high TG patient population to be different in terms of their response to lipid therapy,  
9 including administration of DHA. A person of ordinary skill in the art would have expected that  
10 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with  
11 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a  
12 substantial increase in LDL-C in patients with very high TG levels.

13 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was  
14 known that DHA was responsible for the increase in LDL-C levels.

15 Throughout their contentions, Defendants’ selectively cite to data points in a reference  
16 without considering other disclosures or even the reference as a whole. Each reference,  
17 however, must be evaluated for all that it teaches.<sup>2089</sup> As is the case with Kelley, Defendants use  
18 hindsight to characterize a reference based on LDL-C levels alone without considering the other  
19 lipid effects studied, considered and reported.<sup>2090</sup> The isolated manner in which Defendants  
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<sup>2088</sup> Kelley at 324, 332.

22 <sup>2089</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2090</sup> Kelley at 324 (providing that the objectives of the study were to determine “the effects of DHA supplementation  
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean  
diameters of these particles in fasting and postprandial plasma.”).

1 select such data points is not the approach that a person of ordinary skill would have taken at the  
2 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.  
3 A person of ordinary skill would take into consideration the entire disclosure of a reference,  
4 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,  
5 without explanation, the other effects of DHA that a person of ordinary skill would consider.  
6 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a  
7 favorable effect in hypertriglyceridemic patients.

8 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was  
9 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,  
10 without explanation, other studies that demonstrate that DHA decreases or has little effect on  
11 LDL-C levels.<sup>2091</sup> Defendants identify no other basis upon which a person of ordinary skill  
12 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,  
13 Geppert and/or Kelley.

14 (iv) A Person of Ordinary Skill Would Not Have  
15 been Motivated to Find an Omega-3 Fatty  
16 Acid "Therapy that Would Reduce TG  
17 Levels in Patients with TG Levels  $\geq$ 500  
mg/dL Without Negatively Impacting LDL-  
C Levels."

18 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG  
19 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there  
20 was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,  
21 or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels  
22 for very-high TG patients at the time of the invention. A person of ordinary skill in the art

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24 <sup>2091</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and  
2 Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were  
3 available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription  
4 omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly  
5 undesirable side effects—including “flushing” (or reddening of the face and other areas with a  
6 burning sensation) and dyspepsia—that limited their usefulness.<sup>2092</sup> Fibrates were effective at  
7 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG  
8 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an  
9 LDL-C lowering medication such as a statin.<sup>2093</sup> However, the risk of rhabdomyolysis increased  
10 five-fold if fibrates were administered with a statin.<sup>2094</sup> Therefore, physicians were reluctant to  
11 recommend, and patients were hesitant embrace, a combination fibrate/statin course of  
12 treatment.<sup>2095</sup> Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to  
13 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,  
14 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

15 In any event, a person of ordinary skill in the art would have understood that omega 3-  
16 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high  
17 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would  
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20 <sup>2092</sup> See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 <sup>2093</sup> Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”);

22 <sup>2094</sup> See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 <sup>2095</sup> See *Id.*, ¶ 17

1 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs  
2 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2096</sup>	-20%	+45%
Lovaza/Omacor <sup>2097</sup>	-6%	+45%

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4  
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7 That Epadel has been approved for decades but not approved for use in the very high TG  
8 patient population prior to the invention of the asserted patents is a real-world reflection of the  
9 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
10 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
11 been countless studies conducted which administer Epadel and report the effects observed.  
12 Although a few studies administer Epadel to a patient population which included a few patients  
13 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
14 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

15 Defendants offer no “apparent reason” to administer EPA as claimed to patients with  
16 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on  
17 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients  
18 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”<sup>2098</sup>  
19 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500

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21  
22 <sup>2096</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

23 <sup>2097</sup> Chan 2002 I at 2381 (Table 3).

24 <sup>2098</sup> Defendants’ Joint Invalidity Contentions at 531.

1 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG  
2 reduction and the increased conversion of VLDL to LDL particles.<sup>2099</sup>

3 It was well known at the time of the invention that omega-3 fatty acids, including both  
4 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant  
5 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3  
6 fatty acids worked in part by inhibiting VLDL production and improving the conversion of  
7 VLDL particles to LDL.<sup>2100</sup> A person of ordinary skill in the art understood that EPA and DHA  
8 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when  
9 discussing the TG-lowering mechanism of omega-3 fatty acids.<sup>2101</sup> The discussion related to the  
10 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and  
11 incorporated herein by reference.

12 In fact, it was well understood that the degree of LDL-C elevation observed with  
13 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG  
14 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels  
15 the most in patients with the highest pretreatment TG levels.<sup>2102</sup> Therefore, a person of ordinary  
16 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct  
17 consequence of lowering triglycerides in patients with TG levels  $\geq 500$  mg/dL. The rise in LDL-

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19 <sup>2099</sup> See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese  
20 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and  
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in  
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

21 <sup>2100</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
22 decrease in VLDLs after n-3 fatty acid treatment”)

23 <sup>2101</sup> Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The  
Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

24 <sup>2102</sup> See Bays 2008 Rx Omega-3 p. 402.

1 C was often offset by concurrent treatment with statins.<sup>2103</sup> The safety and efficacy of using  
2 prescription omega-3 in combination with a statin has been well-established.<sup>2104</sup>

3 Although an increase in LDL-C was generally observed when omega-3 fatty acids were  
4 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a  
5 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.

6 Therefore, the final LDL-C concentration may still be in the normal range.<sup>2105</sup> Furthermore, it  
7 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>2106</sup>

8 In two pivotal studies in very-high TG patients, both of which used prospective,  
9 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL  
10 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).<sup>2107</sup> Correspondingly, prescription  
11 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.<sup>2108</sup> Therefore,  
12 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can  
13 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net  
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15 <sup>2103</sup> See Harris 2008 at 14, McKenney at 722.

16 <sup>2104</sup> McKenney at 722-23.

17 <sup>2105</sup> See Westphal at 918, Harris 1997 at 389.

18 <sup>2106</sup> See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals  
with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester  
transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he  
19 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-  
high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the  
20 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute  
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this  
21 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty  
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in  
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by  
22 decreased non-HDL-C levels (TC minus HDL-C”).

23 <sup>2107</sup> McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 <sup>2108</sup> McKenney 2007 at 722 (see Fig. 1).

1 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in  
2 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also  
3 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the  
4 number of small, dense LDL particles to larger LDL particles.<sup>2109</sup> Lovaza/Omacor “adversely  
5 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration  
6 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”<sup>2110</sup>  
7 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3  
8 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not  
9 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention  
10 of [coronary heart disease].”<sup>2111</sup>

11 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at  
12 the time of the claimed inventions would have been motivated to find a therapy that would  
13 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting  
14 LDL-C levels,”<sup>2112</sup> one of ordinary skill in the art at the time of the invention understood that the  
15 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with  
16 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to  
17 increase in very-high TG patients, and in some instances the rise was not concerning because  
18 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final  
19 concentration would still be in the normal range. When LDL-C levels increased beyond what  
20 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

21 \_\_\_\_\_  
22 <sup>2109</sup> McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 <sup>2110</sup> Stalenhoef at 134.

24 <sup>2111</sup> Harris 1997 at 389.

<sup>2112</sup> Defendants’ Joint Invalidation Contentions at 531.

1 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of  
2 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to  
3 identify any other basis upon which a person of ordinary skill would have been motivated to find  
4 a therapy that would reduce TG levels in patients with very-high TG levels without negatively  
5 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood  
6 that EPA therapy would *not* reduce Apo-B<sup>2113</sup> (which is a reflection of total atherogenic  
7 lipoproteins)<sup>2114</sup> in very high TG patients, and accordingly would not have been motivated to  
8 administer the claimed EPA composition to the very high TG patient population.

9 Defendants make the conclusory allegation that “routine optimization” by a person of  
10 ordinary skill would yield the claimed invention.<sup>2115</sup> Defendants, however, have offered no  
11 explanation to support that allegation and they further fail to establish any of the required criteria  
12 of “routine optimization” or the prerequisites to this argument. They also fail to provide any  
13 factual detail to support their allegation and they fail to link the allegation to any particular claim  
14 or claim element. Defendants mere allegation constitute an improper placeholder to later  
15 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,  
16 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the  
17 combinations alleged by Defendants and, for the same reasons, it would not be routine to  
18 combine such references. Where, for example, defendants argue that it would be routine to go  
19 from the high TG patient population to the very high TG patient population,<sup>2116</sup> they provide no  
20 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

21 \_\_\_\_\_  
22 <sup>2113</sup> *see* Section V.O.

23 <sup>2114</sup> *see* Section III.

24 <sup>2115</sup> *See, e.g.*, Defendants’ Joint Invalidity Contentions at 526, 540, 556.

<sup>2116</sup> Defendants’ Joint Invalidity Contentions at 533-34.



1 would have understood these patient populations to be distinct with different impacts of lipid  
2 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would  
3 not have considered the dosage modification suggested by defendants to be routine; Defendants'  
4 argument to the contrary represents hindsight bias.

5 In addition, a person of ordinary skill would have no motivation to combine these  
6 references because EPA would have been expected to have same result as the mixture of EPA  
7 and DHA used in Lovaza/Omacor.

8 (v) A Person of Ordinary Skill Would Not Have  
9 Had a Reasonable Expectation of Success  
10 with the Combinations Defendants  
11 Hypothesize

12 Defendants provide no evidence that a person of ordinary skill would have had a  
13 reasonable expectation of successfully obtaining the claimed invention—a method of reducing  
14 triglycerides in a subject having very-high triglyceride levels by administering EPA of the  
15 recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by  
16 combining the references cited by defendants. For a particular combination of references, there  
17 must be a reasonable expectation that the combination will produce the claimed invention. In  
18 this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with  
19 very-high TG levels.<sup>2117</sup> A person of ordinary skill would have expected EPA, like  
20 Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG  
21 patient population. As discussed in Section III and above, it was well known that TG-lowering

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22 <sup>2117</sup> As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to  
23 have the same TG lowering mechanism and would have further understood that the increase in LDL-C  
24 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of  
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar  
fashion to Lovaza or DHA alone.

1 agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for  
 2 normal to high TG patients, but caused significant increases in LDL-C levels for patients with  
 3 very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary  
 4 skill to expect anything to the contrary. A person of ordinary skill would have understood that  
 5 omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among  
 6 very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2118</sup>	-20%	+45%
Lovaza/Omacor <sup>2119</sup>	-6%	+45%

7  
 8  
 9  
 10  
 11 Accordingly, a person of ordinary skill would *not* have a reasonable expectation of  
 12 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients  
 13 with very-high TG levels.<sup>2120</sup>

14 Defendants’ position that a person of ordinary skill would have had a reasonable  
 15 expectation of success in administering purified EPA to patients with very high triglyceride  
 16 levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that  
 17 Defendants’ provide no evidence that anyone thought to administer Epadel.<sup>2121</sup> Epadel was  
 18 available for many years prior to the invention of the ’399 patent, to patients with very-high TGs  
 19 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,  
 20

21 <sup>2118</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

22 <sup>2119</sup> Chan 2002 I at 2381 (Table 3).

23 <sup>2120</sup> Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall  
 effect on lipid parameters, teaching away from this combination.

24 <sup>2121</sup> Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not  
 examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of  
2 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by  
3 Defendants are directed to the use of purified EPA in the very-high TG population.

4 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
5 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
6 countless studies conducted which administer Epadel and report the effects observed. Although  
7 a few studies administer Epadel to a patient population which included a few patients with TG  
8 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
9 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
10 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
11 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
12 triglycerides.

13 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients  
14 with borderline-high/high TG, it would have been obvious to try administering purified ethyl  
15 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants  
16 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of  
17 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.<sup>2122</sup>  
18 Defendants' contentions are no more than a demonstration that certain claim elements was  
19 known in the prior art and demonstrates impermissible hindsight reconstruction.<sup>2123</sup> As is  
20 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,  
21

22 <sup>2122</sup> Defendants' Joint Invalidation Contentions at 534.

23 <sup>2123</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
24 KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.").

EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably, none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

**TABLE 4**  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>2</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>2</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>2</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>2</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.  
<sup>2</sup>  $\bar{x} \pm$  SD.  
<sup>3-5</sup> One-sample t test of difference between baseline and 7 wk: <sup>3</sup> P < 0.001, <sup>4</sup> P < 0.01, <sup>5</sup> P < 0.05.

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.

1 To the extent that Defendants’ arguments are based on results that are not statistically  
2 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not  
3 draw conclusions from these statistically insignificant differences. Indeed, the standard  
4 deviation for the changes reported is greater than the value of the change itself.

5 Defendants argue that it would have been obvious to try administering purified ethyl EPA  
6 to patients with very-high TG levels with a reasonable expectation of success. However, the  
7 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-  
8 try” proves that the claimed invention was obvious where the prior art did not suggest what to  
9 try.<sup>2124</sup> Rather than there being a limited number of options, the state of the art provided a  
10 plethora of compositions and administration protocols associated with multiple kinds of TG-  
11 lowering therapies.<sup>2125</sup> There were not a finite number of options for a person of ordinary skill  
12 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient  
13 population.

14 Defendants argue that a person of ordinary skill at the time of the invention, based on  
15 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone  
16 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to  
17 no impact on LDL-C levels.<sup>2126</sup> However, that statement does not conform with what was  
18 known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high  
19 TG patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor  
20  
21

22 \_\_\_\_\_  
<sup>2124</sup> See *Sanofi*, 748 F.3d at 1360–61.

23 <sup>2125</sup> See *supra* Section III.

24 <sup>2126</sup> Defendants’ Joint Invalidation Contentions at 533-34.

1 were both known to have little or no effect on LDL-C in patients with borderline-high/high TG  
2 levels.

3 With the lack of any reasonable expectation of success, Defendants argue that their  
4 proposed combination amounts to a simple substitution of one known element for another, and  
5 that that these changes yield predictable results.<sup>2127</sup> Such an argument, however, represents pure  
6 and impermissible hindsight bias and further does not consider that reasons for which a person of  
7 ordinary skill would not be motivated to combine these references and affirmatives ways in  
8 which the art taught away from these combinations.

9 (b) Defendants Have Not Shown It Would Have Been  
10 Obvious to Administer Purified EPA in the Dosing  
Regimen Recited in the Claims

11 (i) The '399 Patent is not Obvious Over WO  
12 '118 or WO '900, in Combination With the  
Lovaza PDR, and Further in View of Leigh-  
13 Firbank and/or Mori 2000

14 With respect to the '399 Patent, Defendants present a combination of five references:  
15 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the  
16 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."<sup>2128</sup> Defendants also  
17 present charts arguing that an additional 61 references may be combined in order to render the  
18 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill  
19 would combine 61 separate references, they additionally do not identify any motivation for  
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23 <sup>2127</sup> Defendants' Joint Invalidation Contentions at 534.

24 <sup>2128</sup> Defendants' Joint Invalidation Contentions at 536.

1 combining these references.<sup>2129, 2130</sup> Although Defendants need not point to an explicit statement  
2 in the prior art motivating the combination of these references, any assertion of an “apparent  
3 reason” to combine must find a basis in the factual record.<sup>2131</sup> Defendants’ unsupported cobbling  
4 of selective disclosures represents hindsight reconstruction.<sup>2132</sup> Defendants’ contentions are no  
5 more than an assertion that certain claim elements were known in the prior art. Throughout their  
6 contentions, Defendants’ selectively cite to data points in a reference without considering other  
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
8

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9  
10 <sup>2129</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more the references cited in  
11 Sections III and V.A. and B., including, the ’954 publication, WO ;900, WO ’118, Ando, Grimsgaard, Hayashi,  
12 Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh,  
13 Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert,  
Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a  
person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to  
meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine  
these references. *See* Defendants’ Joint Invalidity Contentions at 535.

14 <sup>2130</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
15 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
16 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person  
having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 526.

17 <sup>2131</sup> *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point  
21 “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation  
22 to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties  
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.  
Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*  
23 *facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and  
24 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art  
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2132</sup> *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.<sup>2133</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
2 obviousness.

3 WO '118 is directed at the composition containing EPA for the purpose of preventing the  
4 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118  
5 is directed, "in particular, [to] preventing occurrence of cardiovascular events in  
6 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the  
7 risk of the cardiovascular events."<sup>2134</sup> Contrary to Defendants' assertion that WO '118 discloses  
8 "the administration of 4 g of pure EPA with no DHA,"<sup>2135</sup> WO '118 fails to disclose the claimed  
9 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive  
10 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified  
11 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction  
12 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of  
13 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in  
14 the disclosed composition.<sup>2136</sup>

15 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target  
16 population of the claimed invention. The asserted claims are directed to persons with severe  
17 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only  
18 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.<sup>2137</sup> WO  
19 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

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21 <sup>2133</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 <sup>2134</sup> WO '118 at 9.

23 <sup>2135</sup> Defendants' Joint Invalidation Contentions at 536.

24 <sup>2136</sup> WO '118 at 22-23.

<sup>2137</sup> WO '118 at 8.



1 patients with borderline-high to high TG levels, since the primary goal for patients with very-  
2 high TG is to prevent acute pancreatitis by decreasing TG levels.<sup>2138</sup>

3 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the  
4 effectiveness of the substances for treating hypertriglyceridemia.<sup>2139</sup> WO '118 states that  
5 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-  
6 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +  
7 DHA-E) are not particularly limited as long as intended effects of the present invention are  
8 attained.”<sup>2140</sup> It further states that “the composition is preferably the one having a high purity of  
9 EPA-E and DHA-E.”<sup>2141</sup> Further, WO '118 does not disclose EPA’s effect on LDL-C, VLDL-C,  
10 Apo-B, or Lp-PLA2.

11 WO '900 is directed to a process for producing purified EPA from a culture of micro-  
12 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels  
13 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed  
14 pharmaceutical composition with the specified dosage or administration period, or the claimed  
15 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900  
16 only discloses the method of producing purified EPA for therapeutic use, it does not teach  
17 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient  
18 population or method of treatment.

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21 <sup>2138</sup> See Section III.

22 <sup>2139</sup> WO '118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective  
component”).

23 <sup>2140</sup> WO '118 at 22-23.

24 <sup>2141</sup> WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists  
2 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of  
3 them.<sup>2142</sup> Moreover, WO '900 does not teach the desired effect of EPA other than commenting  
4 generally that it “may promote health and ameliorate or even reverse the effects of a range of  
5 common diseases.”<sup>2143</sup> It has no discussion, for example, on any TG-lowering effect of EPA.  
6 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*  
7 undesired effect of DHA or other impurities it is trying to prevent other than commenting  
8 generally that “the desired effects of EPA may be limited or reversed” by them.<sup>2144</sup> It has no  
9 discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claim of the '399 Patent  
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package  
13 insert specifically) during prosecution.<sup>2145</sup>

14 The analysis of the independent claim of the '399 patent is incorporated into all asserted  
15 claims that depend from this claim.

16 (a) Leigh-Firbank and Mori 2000 Do  
17 Not Disclose Purported Knowledge  
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20 <sup>2142</sup> See, e.g., '900 Pub. at 16-17.

21 <sup>2143</sup> '900 Pub. at 5.

22 <sup>2144</sup> '900 Pub. at 39.

23 <sup>2145</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 that DHA was Responsible for the  
2 Increase in LDL-C

3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known  
5 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-  
6 C levels as evidenced by Leigh-Firbank or Mori 2000.”<sup>2146</sup>

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with  
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need  
9 not point to an explicit statement in the prior art motivating the combination of these references,  
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>2147</sup>

11 Defendants’ unsupported cobbling of selective disclosures represents hindsight  
12 reconstruction.<sup>2148</sup> Defendants’ contentions are no more than an assertion that certain claim  
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to  
14 establish *prima facie* obviousness.

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16 <sup>2146</sup> Defendants’ Joint Invalidity Contentions at 536.

17 <sup>2147</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>2148</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that  
2 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank  
3 and Mori 2000 in Section V.D.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank  
4 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and  
5 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does  
6 not offer any disclosure regarding the effect of EPA and DHA separately or gain any  
7 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000  
8 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is  
9 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation  
10 to combine with WO ‘118 or WO ‘900. Engaging in hindsight bias, Defendants ignore, without  
11 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants  
12 fail to identify any other basis upon which a person of ordinary skill would have sought to  
13 combine Mori 2000 with the Lovaza PDR.

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants  
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little  
17 effect on LDL-C levels.<sup>2149</sup> Defendants identify no other basis upon which a person of ordinary  
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or  
19 Mori.

- 20 (ii) The ‘399 Patent is not Obvious Over WO  
21 ‘118, WO ‘900, Grimsgaard, Mori 2000  
22 and/or Maki in Combination with the  
23 Omacor PDR/Lovaza PDR, and Further in

24 <sup>2149</sup> See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '399 Patent, Defendants present a combination of nine references:

“WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku.”<sup>2150</sup> Defendants also present charts arguing that an additional 56 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 56 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>2151</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2152</sup> Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

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<sup>2150</sup> Defendants’ Joint Invalidity Contentions at 536.

<sup>2151</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2152</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
2 even the reference as a whole. Each reference, however, must be evaluated for all that it  
3 teaches.<sup>2153</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
4 obviousness.

5 The discussion related to WO ‘118 and WO ‘900 in Section V.D.3.c.1.b.i is incorporated  
6 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section  
7 V.D.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and  
8 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”  
9 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the  
10 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to  
11 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other  
12 basis upon which a person of ordinary skill would have sought to combine the composition  
13 disclosed in Grimsgaard or Mori 2000.

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art  
15 to use EPA as described in WO ‘118, WO ‘900, Grimsgaard or Mori 2000 in the treatment  
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their  
17 assertions fail to provide a motivation for combining the references.<sup>2154</sup> Although Defendants  
18 need not point to an explicit statement in the prior art motivating the combination of these  
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual  
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22 \_\_\_\_\_  
23 <sup>2153</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>2154</sup> Defendants’ Joint Invalidation Contentions at 537.

1 record.<sup>2155</sup> Defendants’ assertions related to motivation are insufficient,<sup>2156</sup> and accordingly  
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or  
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference  
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the  
6 manner claimed,<sup>2157</sup> or “a reasonable expectation of success”<sup>2158</sup> of achieving the claimed  
7 invention. Therefore, Defendants should be precluded from relying on this these references.

8 As discussed above in Section V.D.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only  
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both  
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12 <sup>2155</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
13 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
14 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
15 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daichi*  
16 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
17 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
18 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
19 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
20 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
21 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
22 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
23 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

24 <sup>2156</sup> For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating  
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any  
basis for that statement. While the paragraph associated with that statement makes assertions regarding the  
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO  
’118. See Defendants’ Joint Invalidity Contentions at 537.

<sup>2157</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

<sup>2158</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

1 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer  
2 purified EPA to the very high TG patient population and do not provide any reasonable  
3 expectation of success in lowering TG levels in the very high TG patient population without  
4 increasing LDL-C. As discussed above in Section V.D.3.c.1.a.ii.a.i, Takaku candidly  
5 acknowledges that “only a few subjects were examined” and cautions against drawing a  
6 conclusion “only from the results of the present study.”<sup>2159</sup> Further, the study did not include any  
7 placebo control, therefore, a person of ordinary skill in the art would understand these reports do  
8 not provide the ability to conclude that the observed lipid effects would have occurred  
9 independent of the drug that is administered. In addition, the study was conducted exclusively in  
10 Japanese patients, and a person of ordinary skill would not have expected the results to be  
11 applicable to the general population.<sup>2160</sup>

12 The proposed combination does not render the independent claim of the '399 Patent  
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and  
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.<sup>2161</sup>

16 The analysis of the independent claim of the '399 patent is incorporated into all asserted  
17 claims that depend from this Claim.

18 (a) Grimsgaard, Mori 2000 and/or Maki  
19 Do Not Disclose Purported  
20 Knowledge that DHA was

21 <sup>2159</sup> Takaku at ICOSAPENT\_DFNDT00006897.

22 <sup>2160</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.”)

23 <sup>2161</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).  
24



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2  
3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known  
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is  
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or  
7 Maki.”<sup>2162</sup>

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose  
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,  
10 Mori 2000 and/or Maki in Section V.D.3.c.1.a.ii.a.iii is incorporated herein by reference. A  
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA  
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,  
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although  
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not  
15 disclose administration of DHA to the requisite patient population and teaches that DHA is  
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,  
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
18 would consider. Most controlled studies in patients with normal to high baseline TG levels  
19 indicated that DHA had little or no effect on LDL-C.<sup>2163</sup> Therefore, a person of ordinary skill  
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline  
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 <sup>2162</sup> Defendants’ Joint Invalidity Contentions at 537.

23 <sup>2163</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG  
2 levels, a significant increase in LDL-C is observed.<sup>2164</sup> However, one of ordinary skill in the art  
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.<sup>2165</sup>  
4 Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion  
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
8 has little effect on LDL-C levels.<sup>2166</sup> Defendants identify no other basis upon which a person of  
9 ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki,  
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

11 (iii) A Person of Ordinary Skill Would Not Have  
12 Been Motivated to Administer Purified EPA  
13 in the Treatment Regimen Recited in the  
14 Claims

15 For an invention to be obvious, there must have been an "apparent reason" to make it.  
16 Defendants assert that a "person of ordinary skill in the art would have been motivated to  
17 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to  
18 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."<sup>2167</sup> However, as  
19 set forth below, Defendants fail to address why a person of ordinary skill in the art would have  
20 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

21 <sup>2164</sup> Maki at 195.

22 <sup>2165</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 ("A number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated fat and cholesterol, both of which are known to elevate LDL-C.").

23 <sup>2166</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>2167</sup> Defendants' Joint Invalidity Contentions at 537.

1 greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering  
2 triglycerides *without increasing LDL-C levels*.

3 Indeed, a person of ordinary skill in the art would have understood that omega 3-fatty  
4 acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG  
5 patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not  
6 have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without  
7 increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2168</sup>	-20%	+45%
Lovaza/Omacor <sup>2169</sup>	-6%	+45%

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12 That Epadel has been approved for decades but not approved for use in the very high TG  
13 patient population prior to the invention of the asserted patents is a real-world reflection of the  
14 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
15 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
16 been countless studies conducted which administer Epadel and report the effects observed.  
17 Although a few studies administer Epadel to a patient population which included a few patients  
18 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
19 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

20 Defendants further argue that the disclosure in WO '118 would combine with the prior art  
21 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to

22  
23 <sup>2168</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>2169</sup> Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118  
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-  
3 purified ethyl-EPA.”<sup>2170</sup> Both of the “reasons” identified by Defendants are false.

4       Regarding Defendants’ first reason, that “products containing DHA were reported to  
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in  
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on  
7 LDL-C.<sup>2171</sup> Therefore, a person of ordinary skill would not have concluded that DHA increases  
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,  
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,  
10 while EPA does not.”<sup>2172</sup> First, Leigh-Firbank cannot comment on the effect of EPA and DHA  
11 alone because it did not administer EPA and DHA separately.<sup>2173</sup> A person of ordinary skill  
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect  
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA  
14 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with  
15 other saturated and polyunsaturated fatty acids.<sup>2174</sup> Therefore, a person of ordinary skill would  
16 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear  
17 how much of the supplement’s effects can be attributed to DHA.<sup>2175</sup> Kelley does not show that

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<sup>2170</sup> Defendants’ Joint Invalidity Contentions at 538.

20 <sup>2171</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
21 controlled, found an increase in LDL-C after DHA administration.

22 <sup>2172</sup> Defendants’ Joint Invalidity Contentions at 542.

23 <sup>2173</sup> The discussion related to Leigh-Firbank in Section V.D.3.c.1.a.i.a.iii is incorporated herein by reference.

24 <sup>2174</sup> The discussion related to Kelley in Section V.D.3.c.1.a.iii.a.ii is incorporated herein by reference.

<sup>2175</sup> See Mori 2006 at 96.

1 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a  
2 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase  
3 was induced by fibrate therapy.<sup>2176</sup> Kelley specifically teaches that the increase in LDL-C  
4 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel  
5 increase in overall LDL particle number. Rather than concluding that DHA was uniquely  
6 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to  
7 disclose that DHA had uniquely beneficial cardioprotective effects.<sup>2177</sup> Finally, Theobald also  
8 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for  
9 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by  
10 7% when compared to placebo. However, the DHA composition that was administered in  
11 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,  
12 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA  
13 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it  
14 impossible to determine whether or how much of the supplement’s effects can be attributed to  
15 DHA.<sup>2178</sup> Contrary to Defendants’ assertion that there was “a reported advantage to using EPA  
16 vs. DHA in hypertriglyceridemic subjects,”<sup>2179</sup> there was no known advantage to using EPA vs.  
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately  
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after  
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20 <sup>2176</sup> Kelley at 329.

21 <sup>2177</sup> Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”  
and that “DHA supplementation may improve cardiovascular health.”)

23 <sup>2178</sup> See Mori 2006 at 96.

24 <sup>2179</sup> Defendants’ Joint Invalidity Contentions at 538.

1 EPA supplementation.”<sup>2180</sup> In addition, a person of ordinary skill would have recognized any  
2 impact of DHA reported by the study to be applicable to EPA because they would have  
3 understood these substances to function by the same mechanism. Furthermore, as discussed  
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in  
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients  
6 because patients with higher TG levels had different lipid responses compared to patients with  
7 lower TG levels.

8       Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in  
9 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”  
10 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been  
11 well documented.<sup>2181</sup> Lovaza/Omacor has been shown to reduce the risk for cardiovascular  
12 death plus nonfatal myocardial infarction and nonfatal stroke.<sup>2182</sup> Omega-3 fatty acids have been  
13 shown to exert cardioprotective effects in both primary and secondary coronary heart disease  
14 prevention trials.<sup>2183</sup> Omega-3 fatty acids were known to reduce TG concentration, have  
15 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure  
16 and/or reduce heart rate.<sup>2184</sup>

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19 <sup>2180</sup> Mori 2000 at 1092.

20 <sup>2181</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA  
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 <sup>2182</sup> See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,  
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

22 <sup>2183</sup> Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,  
197 Atherosclerosis 12, 13 (2008) (“Harris 2008”).

23 <sup>2184</sup> Harris 2008 at 13.

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1 Defendants argue that a “person of ordinary skill in the art would have appreciated the  
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce  
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of  
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”<sup>2185</sup> As  
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA  
6 and Lovaza/Omacor have been well documented.<sup>2186</sup>

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart  
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that  
9 DHA is *more* cardioprotective than EPA.<sup>2187</sup> This study found that “depressed levels of long-  
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary  
11 heart disease events.”<sup>2188</sup> Further, the study found that DHA levels, with or without EPA, were  
12 significantly lower in fatal endpoints.<sup>2189</sup> This study suggests that DHA is preferable to EPA—  
13 thus teaching away from the claimed invention.<sup>2190</sup> Defendants rely on hindsight bias to argue  
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA  
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16 <sup>2185</sup> Defendants’ Joint Invalidity Contentions at 538-39.

17 <sup>2186</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA  
18 and CHD risk.”) (“Harris 2007”).

19 <sup>2187</sup> Harris 2007 at 8.

20 <sup>2188</sup> *Id.*

21 <sup>2189</sup> Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all  
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 <sup>2190</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of  
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the  
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*  
*Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs.,*  
*Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the  
prior art ... is strong evidence of nonobviousness.”).

1 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA  
2 was *more* cardioprotective than EPA.

3 Defendants argue that the following claim elements were known: the administration of  
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the  
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to  
6 patients with high and very high TG levels who were not receiving concurrent lipid altering  
7 therapy, and the dose of 4g/day and 12-week regimen.<sup>2191</sup> Defendants then argue that the “only  
8 question is whether one skilled in the art would have been motivated to use the DHA-free,  
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at  
10 least 500 mg/dL as part of the claimed dosage regimen.”<sup>2192</sup>

11 Defendants’ contentions are no more than a recitation that certain claim elements were  
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight  
13 reconstruction.<sup>2193</sup> Notably, Defendants *do not* assert that a person of ordinary skill would have  
14 known that purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL),  
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,<sup>2194</sup>  
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a  
17 number of prior art references disclosed the administration of purified EPA to patients with TG  
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20 <sup>2191</sup> Defendants’ Joint Invalidity Contentions at 546.

21 <sup>2192</sup> Defendants’ Joint Invalidity Contentions at 540.

22 <sup>2193</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 <sup>2194</sup> Nakamura, Matsuzawa, and Takaku.



1 levels > 500 mg/dL.”<sup>2195,2196</sup> The disclosures of Nakamura (one patient), Matsuzawa (disclosure  
2 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the  
3 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of  
4 ordinary skill in the art would *not* understand these references to relate to the use of EPA in  
5 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions  
6 regarding these references in terms of the very high TG patient population. In Nakamura, one  
7 patient had a baseline TG level > 500 mg/dL.<sup>2197</sup> However, the mean baseline TG for all patients  
8 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was  
9 well below 500 mg/dL.<sup>2198</sup> In Matsuzawa, three patients had TG levels between 400 and 1000  
10 mg/dL and one patient had TG levels > 1,000 mg/dL.<sup>2199</sup> Based on this disclosure, only one  
11 patient definitively had a baseline TG level  $\geq$  500 mg/dL. Further, this one patient was excluded  
12 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol  
13 made it impossible to assess triglyceride levels.”<sup>2200</sup> In Takaku, three patients had baseline TG  
14 levels above 500 mg/dL.<sup>2201</sup> However, the mean baseline TG level for all patients was 245  
15 mg/dL.<sup>2202</sup> Indeed, the mean baseline TG level of the patients in all three studies was well below  
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17 <sup>2195</sup> Defendants’ Joint Invalidation Contentions at 539.

18 <sup>2196</sup> Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500  
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually  
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumura specifically  
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 <sup>2197</sup> Nakamura at 23, Table 1.

23 <sup>2198</sup> Nakamura at 23, Tables 1 and 2.

24 <sup>2199</sup> *Id.* at 23.

<sup>2200</sup> *Id.* at 10.

<sup>2201</sup> Takaku at ICOSAPENT\_DFNDTS00006895.

<sup>2202</sup> Takaku at ICOSAPENT\_DFNDTS00006875.

1 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be  
2 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,  
3 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the  
4 Friedewald's Equation cannot be used for patients with triglyceride levels  $\geq$  400 mg/dL.<sup>2203</sup>  
5 Defendants have failed to identify all of the claimed elements and fail to provide motivation to  
6 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with  
7 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated  
9 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the  
10 known TG-lowering effects of highly-purified EPA-E."<sup>2204</sup> This argument is flawed. The prior  
11 art demonstrates a wide range of administration periods utilized in different clinical studies. For  
12 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in  
13 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.  
14 Given the large number of choices of administration periods disclosed in prior art, Defendants  
15 have not shown that a person of ordinary skill would not have been motivated to administer  
16 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

17 Moreover, a person of ordinary skill would not have been motivated to administer highly-  
18 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as  
19 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood  
20 triglycerides.<sup>2205</sup> In fact, Defendants acknowledge in their Joint Invalidity Contentions that

21  
22 <sup>2203</sup> See Matsuzawa at ICOSAPENT\_DFNDTS00006450.

23 <sup>2204</sup> Defendants' Joint Invalidity Contentions at 540.

24 <sup>2205</sup> Mori 2006 at 98.

1 “DHA and EPA were both known to comparably reduce triglycerides, independently of one  
2 another.”<sup>2206</sup> Data from some studies even suggested that DHA or fish oil may reduce  
3 triglyceride more effectively than EPA.<sup>2207</sup> Therefore, a person of ordinary skill would not have  
4 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination  
5 of EPA and DHA (such as Lovaza) for 12 weeks.

6 Defendants argue that a “person of ordinary skill in the art also would have been  
7 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant  
8 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.<sup>2208</sup> This  
9 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with  
10 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to  
11 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

12 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have  
13 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such  
14 as Lovaza).

15 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses  
16 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of  
17 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a  
18 dose of 4 g/day rather than a lower dose.”<sup>2209</sup> A person of ordinary skill would not have relied  
19 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,

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21 <sup>2206</sup> Defendants’ Joint Invalidation Contentions at 544.

22 <sup>2207</sup> Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor  
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was  
23 grater with DHA supplementation than EPA supplementation).

24 <sup>2208</sup> Defendants’ Joint Invalidation Contentions at 540.

<sup>2209</sup> Defendants’ Joint Invalidation Contentions at 540-41.

1 because these studies were not designed to determine the effect of dose on the degree of TG  
2 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower  
3 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

4 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood  
5 triglycerides.<sup>2210</sup> Therefore, a person of ordinary skill would not have been motivated to  
6 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of  
7 EPA and DHA (such as Lovaza).

8 Defendants further argue that a “person of ordinary skill in the art would have also been  
9 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with  
10 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much  
11 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito  
12 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”<sup>2211</sup> This  
13 argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a  
14 greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill  
15 would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any  
16 other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects  
17 having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have  
18 expected that a greater decrease in TG levels, in the very high TG patient population, would lead  
19 to a greater increase in LDL-C levels.

20 Defendants contend that a “person of ordinary skill in the art would have been motivated  
21 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a

22 \_\_\_\_\_  
23 <sup>2210</sup> See Section III.

24 <sup>2211</sup> Defendants’ Joint Invalidity Contentions at 541.

1 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to  
2 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”<sup>2212</sup> Defendants first  
3 support this argument by asserting that a person of ordinary skill in the art would have known  
4 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is  
5 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA  
6 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,  
7 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in  
8 V.B.4. and 5” to support this proposition,<sup>2213</sup> however these references do not disclose or suggest  
9 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very  
10 high TG patients.<sup>2214</sup>

11 Defendants next argue again that DHA was known to be responsible for the increase in  
12 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of  
13 ordinary skill would understand that both EPA and DHA function similarly, and that both would  
14 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would  
15 increase LDL-C levels in patients with very high TGs.

16 Defendants argue that a person of ordinary skill in the art “would have known that an  
17 increase in LDL-C was an adverse health effect to be avoided.”<sup>2215</sup> While an increase in LDL-C  
18 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that  
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<sup>2212</sup> Defendants’ Joint Invalidation Contentions at 542.

22 <sup>2213</sup> Defendants’ Joint Invalidation Contentions at 542.

23 <sup>2214</sup> *See* Section IV.

24 <sup>2215</sup> Defendants’ Joint Invalidation Contentions at 544.

1 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3  
2 fatty acids generally, was related to increased conversion of VLDL to LDL particles.<sup>2216</sup>

3 Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the  
4 art would have been motivated, with a reasonable expectation of success, to administer a highly-  
5 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in  
6 LDL-C with DHA.”<sup>2217</sup> However, a person of ordinary skill in the art expected an increase in  
7 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time  
8 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant  
9 decrease in the production of VLDL particles and a significant increase in the conversion of  
10 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by  
11 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.<sup>2218</sup> A  
12 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering  
13 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering  
14 mechanism of omega-3 fatty acids.<sup>2219</sup> The discussion related to the TG-lowering mechanism of  
15 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

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20 <sup>2216</sup> See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription  
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly  
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride  
23 levels when given prescription omega-3 therapy”); Chan 2003.

24 <sup>2217</sup> Defendants’ Joint Invalidity Contentions at 544.

<sup>2218</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”).

<sup>2219</sup> Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

1 Further, a person of ordinary skill in the art would have understood that EPA therapy  
2 would *not* reduce Apo-B<sup>2220</sup> (which is a reflection of total atherogenic lipoproteins)<sup>2221</sup> in very  
3 high TG patients, and accordingly would not have been motivated to administer the claimed EPA  
4 composition to the very high TG patient population.

5 Accordingly, a person of ordinary skill would not have been motivated to combine WO  
6 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and  
7 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not  
8 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-  
9 Firbank and/or Mori 2000.

10 (iv) A Person of Ordinary Skill Would Not Have  
11 Had a Reasonable Expectation of Success  
12 with the Combinations Defendants  
Hypothesize

13 Defendants contend that a “person of ordinary skill in the art would have been motivated  
14 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal  
15 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>2222</sup>

16 Defendants also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . .  
17 would have given a person of ordinary skill in the art a reasonable expectation of successfully  
18 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in  
19 these subjects relative to baseline or placebo.”<sup>2223</sup> However, Defendants provide no evidence  
20 that a person or ordinary skill would have had a reasonable expectation of success in a method of

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22 <sup>2220</sup> *see* Section V.O.

23 <sup>2221</sup> *see* Section III.

24 <sup>2222</sup> Defendants’ Joint Invalidation Contentions at 537.

<sup>2223</sup> Defendants’ Joint Invalidation Contentions at 541 . . .

1 reducing triglycerides in a subject having very-high triglyceride levels by administering purified  
2 EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore,  
3 Defendants fail to provide a reasonable expectation of success for the claimed invention.

4 Defendants further argue, that “because it was known that DHA and EPA were  
5 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have  
6 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified  
7 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been  
8 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition  
9 with a reasonable expectation of success that such administration would result in reducing  
10 triglycerides while avoiding an increase in LDL.”<sup>2224</sup> Defendants argument is without any basis.  
11 To the contrary, because a person of ordinary skill in the art would have understood DHA and  
12 EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have  
13 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no  
14 explanation and cite to no article to support their argument that the similar effects on TG levels is  
15 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on  
16 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected  
17 *both* EPA and DHA, whether administered alone or in combination, would cause an increase in  
18 LDL-C when administered to the very high TG patient population.

19 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients  
20 with very-high TG. A person of ordinary skill would have thus expected EPA, like  
21 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient  
22 population. It was well known that TG-lowering agents, specifically fibrates and  
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24 <sup>2224</sup> Defendants’ Joint Invalidity Contentions at 545.



1 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but  
 2 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art  
 3 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the  
 4 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including  
 5 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as  
 6 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2225</sup>	-20%	+45%
Lovaza/Omacor <sup>2226</sup>	-6%	+45%

7  
 8  
 9  
 10  
 11 Accordingly, a person of ordinary skill would not have a reasonable expectation of  
 12 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients  
 13 with very-high TG levels using EPA.

14 Defendants' position that a person of ordinary skill would have had a reasonable  
 15 expectation of success in administering purified EPA to the requisite patient population to  
 16 achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that  
 17 Defendants' provide no evidence that anyone thought to administer Epadel, which was available  
 18 for many years prior to the invention of the '399 patent, to patients with very-high TGs as a  
 19 treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified  
 20 EPA in the very-high TG population.

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 22  
 23 <sup>2225</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>2226</sup> Chan 2002 I at 2381 (Table 3).

1 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
2 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
3 countless studies conducted which administer Epadel and report the effects observed. Although  
4 a few studies administer Epadel to a patient population which included a few patients with TG  
5 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
6 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
7 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
8 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
9 triglycerides.

10 Accordingly, a person of ordinary skill would not have a reasonable expectation of  
11 success in achieving the claimed invention.

12 (2) Dependent Claims

13 (a) Defendants Have Not Shown that Claim 2 of the  
14 '399 Patent Would Have Been Obvious

15 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
16 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
17 by clear and convincing evidence, they also have not adequately proven the obviousness of  
18 Claim 2.

19 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach  
20 the additional claim elements of dependent Claim 2. Defendants contend, without providing any  
21 support, that the claim elements are the results of simply optimizing the conditions described in  
22 the prior art and within the purview of the skilled physicians. These contentions: 1) do not  
23 assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an  
24 obvious analysis; 3) fail to address whether the specific combination of claim elements were all

1 present in the prior art references that would have been combined by a person of ordinary skill in  
2 the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to  
3 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the  
4 claim element to the point of reading the element out of the claim. Although convenient and  
5 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,  
6 the law of claim construction, or the law of obviousness.

7 Defendants fail to show a specific combination of references that discloses each element  
8 of the claimed invention. None of the cited references discloses administration of the claimed  
9 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
10 combined to teach the administration of the claimed EPA to very high TG patients.<sup>2227</sup>

11 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
12 considering other disclosures or even the reference as a whole. Each reference, however, must  
13 be evaluated for all that it teaches.<sup>2228</sup> Defendants' unsupported cobbling of selective disclosures  
14 represents hindsight reconstruction.<sup>2229</sup>

15 Defendants fail to show a motivation or reason to combine or modify the references  
16 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
17 "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not  
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20 <sup>2227</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
21 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art").

22 <sup>2228</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2229</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention").

1 show why a person of ordinary skill would have been motivated to combine the references to  
2 achieve the claimed invention.<sup>2230</sup>

3 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
4 have successfully achieved the claimed invention. In fact, other than simply identifying prior art  
5 references that purportedly disclose disparate elements, Defendants do not even discuss whether  
6 a person of ordinary skill would have expected that the combination to work for its intended  
7 purpose.<sup>2231</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
8 claimed invention.

9 (b) Defendants Have Not Shown that Claim 3 of the  
10 '399 Patent Would Have Been Obvious

11 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
12 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
13 by clear and convincing evidence, they also have not adequately proven the obviousness of  
14 Claim 3.

15 Defendants contend, without providing meaningful support, that the claim element was  
16 well known in the art. These contentions: 1) do not assert what the prior art discloses to a  
17 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address  
18 whether the specific combination of claim elements were all present in the prior art references  
19 that would have been combined by a person of ordinary skill in the art to produce the claimed

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21 <sup>2230</sup>*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>2231</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*  
2 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
3 point of reading the element out of the claim. Although convenient and expedient, Defendants'  
4 approach does not conform with the Local Patent Rules of this District, the law of claim  
5 construction, or the law of obviousness.

6 Defendants fail to show a specific combination of references that discloses each element  
7 of the claimed invention. Defendants make a conclusory statement that the claimed method of  
8 treatment was well known in the art, but such a naked assertion does not show why a person of  
9 ordinary skill would have been motivated to combine the references to achieve the claimed  
10 invention.<sup>2232</sup> Further Defendants cite to the “Lovaza product” without identifying the prior art  
11 reference to which they refer. Such a reference is inadequate.

12 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
13 have successfully achieved the claimed invention. Defendants do not even discuss whether a  
14 person of ordinary skill would have expected that the combination to work for its intended  
15 purpose.<sup>2233</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
16 claimed invention.

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20 <sup>2232</sup>*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
21 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,  
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>2233</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 (c) Defendants Have Not Shown that Claim 4 of the  
2 '399 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
4 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
5 by clear and convincing evidence, they also have not adequately proven the obviousness of  
6 Claim 4.

7 Defendants contend that it would be obvious that a person receiving the claimed EPA  
8 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50  
9 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean  
10 LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for  
11 the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) fail to  
12 address whether the specific combination of claim elements were all present in the prior art  
13 references that would have been combined by a person of ordinary skill in the art to produce the  
14 claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie*  
15 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
16 point of reading the element out of the claim. Although convenient and expedient, Defendants'  
17 approach does not conform with the Local Patent Rules of this District, the law of claim  
18 construction, or the law of obviousness.

19 Defendants fail to show a specific combination of references that discloses each element  
20 of the claimed invention. Defendants merely demonstrate that the element was purported known  
21 in the prior art without explaining how it can be combined with other elements.<sup>2234</sup> As such,

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23 <sup>2234</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
24 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

1 Defendants discuss the claim element in isolation, and fail to address the claimed invention as a  
2 whole.<sup>2235</sup> Defendants selectively cite to an unspecified isolated disclosure within a reference  
3 without considering other disclosures or even the reference as a whole. Each reference,  
4 however, must be evaluated for all that it teaches.<sup>2236</sup> Defendants’ unsupported cobbling of  
5 selective disclosures represents hindsight reconstruction.<sup>2237</sup>

6 Because Defendants do not identify any combination of references, they necessarily fail  
7 to offer any evidence that a person of skill in the art would be motivated to combine those  
8 references in order to achieve the invention of the claim as a whole. Further, Defendants do not  
9 discuss at all whether a person of ordinary skill would have been motivated to combine the  
10 elements, other than stating that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or  
11 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment.  
12 Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150  
13 mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs  
14 note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40  
15 mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would  
16 have been motivated to combine the elements to achieve the claimed invention.<sup>2238</sup>

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19 <sup>2235</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

20 <sup>2236</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>2237</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 <sup>2238</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
24 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Similarly, without the disclosure of a combination of references and a motivation/reason  
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
3 person of ordinary skill in the art would have had a reasonable expectation of success in  
4 achieving the claimed invention. In fact, other than simply identifying prior art references that  
5 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
6 ordinary skill would have expected that the combination to work for its intended purpose for  
7 treating the recited patient population.<sup>2239</sup> As such, Defendants fail to demonstrate reasonable  
8 expectation of success of the claimed invention.

9 (d) Defendants Have Not Shown that Claim 5 of the  
10 '399 Patent Would Have Been Obvious

11 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
12 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
13 by clear and convincing evidence, they also have not adequately proven the obviousness of  
14 Claim 5.

15 Defendants do not identify any combination of references and simply provide a laundry  
16 list of references without explaining how each reference relates to the claimed invention.  
17 Defendants further contend, without any support, that a person of ordinary skill would have been  
18 able to determine the patient population in need of the claimed methods of treatment, would seek  
19 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat  
20 those patients having very high triglycerides regardless of the baseline values of these lipids.<sup>2240</sup>  
21 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in

22 <sup>2239</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
24 combined, but also that the combination would have worked for its intended purpose.”)

<sup>2240</sup> *Id.*



1 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
2 combination of claim elements were all present in the prior art references that would have been  
3 combined by a person of ordinary skill in the art to produce the claimed invention with a  
4 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
5 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
6 element out of the claim. Although convenient and expedient, Defendants' approach does not  
7 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
8 obviousness.

9 Defendants fail to show a specific combination of references that discloses each element  
10 of the claimed invention. Defendants merely list references, without reference to a specific page  
11 or section, that purportedly disclose disparate elements without explaining how they can be  
12 combined.<sup>2241</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
13 the claimed invention as a whole.<sup>2242</sup> Moreover, by simply identifying prior art references  
14 without discussing the specific teachings of each reference, Defendants fail to consider each  
15 prior art reference as a whole.<sup>2243</sup> Each reference must be evaluated for all that it teaches.

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20 <sup>2241</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

21 <sup>2242</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 <sup>2243</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit.”) (internal citation and quotation marks omitted).

1 Defendants' unsupported cobbling of selective disclosures represents hindsight  
2 reconstruction.<sup>2244</sup>

3 Because Defendants do not identify any combination of references, they necessarily fail  
4 to offer any evidence that a person of skill in the art would be motivated to combine those  
5 references in order to achieve the invention of the claim as a whole. Defendants make a  
6 conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed  
7 methods of treatment, without providing a reason that would have prompted a person of ordinary  
8 skill to combine the elements.<sup>2245</sup> Such a naked assertion does not show why a person of  
9 ordinary skill would have been motivated to treat the recited patient population using the claimed  
10 methods of treatment.<sup>2246</sup>

11 Similarly, without the disclosure of a combination of references and a motivation/reason  
12 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
13 person of ordinary skill in the art would have had a reasonable expectation of success in  
14 achieving the claimed invention. In fact, other than simply identifying prior art references that  
15 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
16 ordinary skill would have expected that the combination to work for its intended purpose for  
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18 <sup>2244</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
19 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention").

20 <sup>2245</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be  
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted)

22 <sup>2246</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR*  
23 Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry,  
the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill  
24 in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness  
determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 treating the recited patient population.<sup>2247</sup> As such, Defendants fail to demonstrate reasonable  
2 expectation of success of the claimed invention.

3 (e) Defendants Have Not Shown that Claims 6 and 7 of  
4 the '399 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
6 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
7 by clear and convincing evidence, they also have not adequately proven the obviousness of  
8 Claims 6 and 7.

9 Defendants contend, without support, that the recited reduction in TG represents  
10 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to  
11 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of  
12 ordinary skill to seek to reduce TG by the recited amount because there is no significance  
13 attached to the amount. Defendants conclude, without support, that there was a reasonable  
14 expectation of success without identifying any combination of references and without explaining  
15 how each reference relates to the claimed invention.<sup>2248</sup> These contentions: 1) do not assert  
16 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious  
17 analysis; 3) fail to address whether the specific combination of claim elements were all present in  
18 the prior art references that would have been combined by a person of ordinary skill in the art to  
19 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish

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21 <sup>2247</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
22 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
23 combined, but also that the combination would have worked for its intended purpose.”)

24 <sup>2248</sup> Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris\_Etherton 2002, Kurabayashi, Leigh-  
Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney  
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,  
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim  
2 element to the point of reading the element out of the claim. Although convenient and expedient,  
3 Defendants’ approach does not conform with the Local Patent Rules of this District, the law of  
4 claim construction, or the law of obviousness.

5 Defendants further contend, without support, that a person of ordinary skill would  
6 “reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation  
7 containing no DHA,” as a formulation containing both EPA and DHA. Defendants conclude,  
8 without support, that it would have been obvious to administer a composition containing EPA,  
9 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while  
10 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to  
11 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim  
12 elements were all present in the prior art references that would have been combined by a person  
13 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of  
14 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
15 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
16 Although convenient and expedient, Defendants’ approach does not conform with the Local  
17 Patent Rules of this District, the law of claim construction, or the law of obviousness.

18 Defendants do not identify any combination of references and simply provide a laundry  
19 list of references that purportedly disclose disparate elements without explaining how they can  
20 be combined.<sup>2249</sup> As such, Defendants discuss the claim elements in isolation, and fail to address

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23 <sup>2249</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*  
24 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

1 the claimed invention as a whole.<sup>2250</sup> Defendants selectively cite to an unspecified isolated  
2 disclosure within a reference without considering other disclosures or even the reference as a  
3 whole. Each reference, however, must be evaluated for all that it teaches.<sup>2251</sup> Defendants'  
4 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2252</sup>

5 Because Defendants do not identify any combination of references, they necessarily fail  
6 to offer any evidence that a person of skill in the art would be motivated to combine those  
7 references in order to achieve the invention of the claim as a whole. Defendants make a  
8 conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to  
9 reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a  
10 person of ordinary skill to reduce triglycerides by the recited amount.<sup>2253</sup> Defendants' burden to  
11 establish *prima facie* obviousness is not discharged because there is allegedly "no significance"

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16 <sup>2250</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim").

17 <sup>2251</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

18 <sup>2252</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention").

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20 <sup>2253</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 attached to the recited TG reduction amount.<sup>2254</sup> Defendants have not met the burden with the  
2 naked assertion that it would have been obvious to seek the claim element.

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. Defendants make a conclusory statement that there was a  
7 reasonable expectation of success, without providing a support other than merely identifying  
8 prior art references that purportedly disclose disparate elements.<sup>2255</sup> The mere fact that elements  
9 are capable of being physically combined does not establish reasonable expectation of  
10 success.<sup>2256</sup>

11 (f) Defendants Have Not Shown that Claim 8 of the  
12 ‘399 Patent Would Have Been Obvious

13 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
14 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
15 by clear and convincing evidence, they also have not adequately proven the obviousness of  
16 Claim 8.

17 Defendants offer no reference in support of their contention that this claim is obvious.  
18 Defendants contend, without providing any support, that it would be obvious to one of skill in

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19 <sup>2254</sup> Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been  
20 established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*  
case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

21 <sup>2255</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
22 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted).

23 <sup>2256</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”).

1 the art to administer a composition containing EPA, but containing no DHA, with a reasonable  
2 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These  
3 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;  
4 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of  
5 claim elements were all present in the prior art references that would have been combined by a  
6 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation  
7 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
8 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
9 Although convenient and expedient, Defendants' approach does not conform with the Local  
10 Patent Rules of this District, the law of claim construction, or the law of obviousness.

11 Defendants fail to show a specific combination of references that discloses each element  
12 of the claimed invention. None of the cited references discloses administration of the claimed  
13 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
14 combined to teach the administration of the claimed EPA to very high TG patients.<sup>2257</sup>  
15 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
16 considering other disclosures or even the reference as a whole. Each reference, however, must  
17 be evaluated for all that it teaches.<sup>2258</sup> Defendants' unsupported cobbling of selective disclosures  
18 represents hindsight reconstruction.<sup>2259</sup>

19  
20 <sup>2257</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

21  
22 <sup>2258</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2259</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

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1 Defendants fail to show a motivation or reason to combine or modify the references  
2 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
3 would have been obvious but such a naked assertion does not show why a person of ordinary  
4 skill would have been motivated to combine the references to achieve the claimed invention.<sup>2260</sup>

5 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
6 have successfully achieved the claimed invention. In fact, Defendants do not even discuss  
7 whether a person of ordinary skill would have expected that the combination to work for its  
8 intended purpose.<sup>2261</sup> As such, Defendants fail to demonstrate reasonable expectation of success  
9 of the claimed invention.

10 Defendants cite only one reference in their invalidity contentions with respect to this  
11 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,  
12 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of  
13 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument  
14 and no support for their argument that Theobald makes such a disclosure. Defendants appear to  
15 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all  
16 atherogenic lipoproteins.<sup>2262</sup>

17 Defendants then make the unsupported assertion that “one of ordinary skill in the art  
18 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to

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19  
20 <sup>2260</sup>*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

21  
22 <sup>2261</sup>*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
23 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

24 <sup>2262</sup> June 26, 2012 Bays Declaration; *see also* Section III.



1 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald  
 2 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render  
 3 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis  
 4 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL  
 5 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with  
 6 respect to this claim or Apo-B levels.

7 As discussed above, *see* Section IV, Theobald discloses the administration of a  
 8 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While  
 9 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a  
 10 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of  
 11 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to  
 12 consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following  
 13 administration of the triacylglycerol composition of that reference.<sup>2263</sup>

14 **TABLE 3**  
 15 Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect <sup>1</sup>
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 <sup>2</sup>	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) <sup>3</sup>
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) <sup>4</sup>
HDL cholesterol (mmol/L) <sup>5</sup>	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) <sup>6</sup>	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
<b>Apolipoprotein B (g/L)</b>	<b>0.84 ± 0.027</b>	<b>0.87 ± 0.026</b>	<b>0.83 ± 0.028</b>	<b>0.84 ± 0.028</b>	<b>0.03 (0.002, 0.055)<sup>7</sup></b>
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) <sup>3</sup>
Weight (kg) <sup>8</sup>	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

19 <sup>1</sup> Mean difference between active treatment and placebo; 95% CI in parentheses.

20 <sup>2</sup>  $\bar{x} \pm \text{SEM}$  (all such values);  $n = 38$ .

21 <sup>3,4,7</sup> Paired  $t$  test: <sup>3</sup> $P = 0.04$ , <sup>4</sup> $P = 0.004$ , <sup>7</sup> $P = 0.03$ .

22 <sup>5</sup> HDL increased in subjects receiving DHA first. Significant treatment  $\times$  order effect,  $P = 0.005$ .

23 <sup>6</sup>  $n = 37$ ; data were log transformed before analysis by paired  $t$  test.

24 <sup>8</sup> Weight increased over the entire study period. Significant order  $\times$  time effect,  $P = 0.001$ .

<sup>2263</sup> Theobald at 561, table 3.

1 As discussed above, *see* Section III, a person of skill in the art would not have  
2 distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a  
3 person of ordinary skill would have considered Theobald, they would not conclude from the  
4 reference that EPA therapy decreases Apo-B levels in very high TG patients.

5 A person of skill in the art would *not* have understood that EPA therapy in very high TG  
6 patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked  
7 to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on  
8 Apo-B levels in patients with very high TG levels.<sup>2264</sup> The Lovaza clinical trial, which was a  
9 large study conducted on patients with very high TG levels, shows no difference between a  
10 placebo-control group and the treatment group with respect to Apo-B levels.<sup>2265</sup>

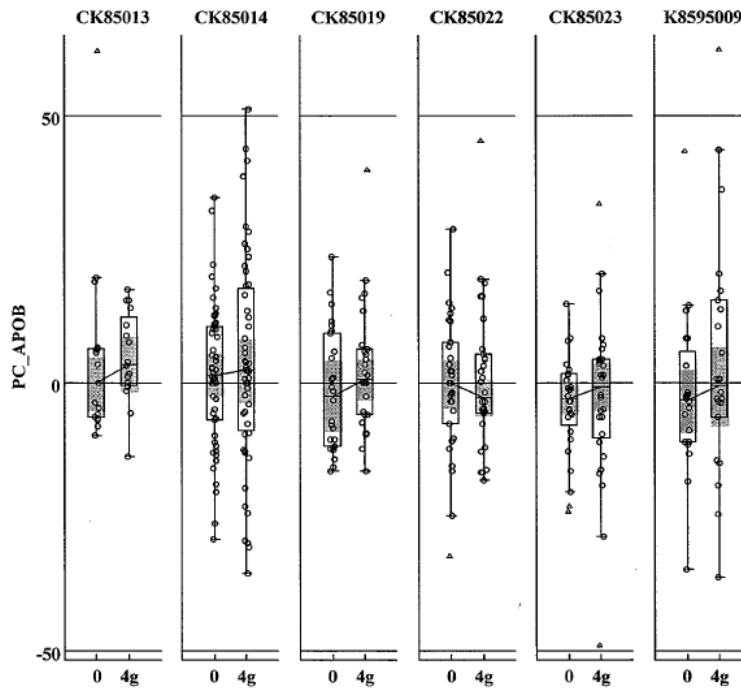
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<sup>2264</sup> May 8, 2012 Bays Declaration.

<sup>2265</sup> Lovaza Approval Package at Table 14.

14. Box plot of individual Category I studies -% change of APOB

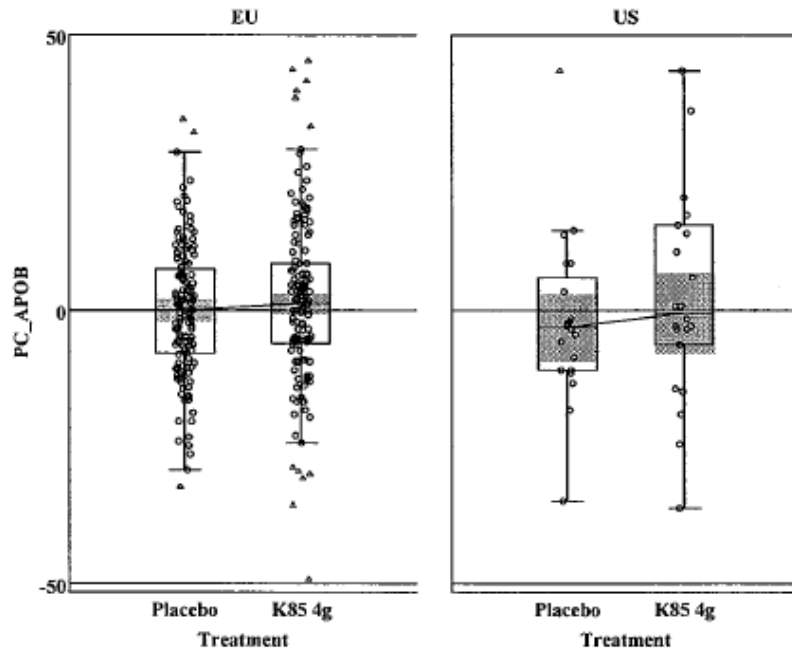


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,<sup>2266</sup> there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza did not impact Apo-B compared to placebo.<sup>2267</sup>

<sup>2266</sup> The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

<sup>2267</sup> Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.<sup>2268</sup> While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

<sup>2268</sup> See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of  
2 success.<sup>2269</sup>

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the  
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.<sup>2270</sup> The person of  
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels  
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As  
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic  
8 lipoproteins, but instead smaller, denser particles referred to as remnant.<sup>2271</sup> Accordingly,  
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because  
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of  
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients  
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to  
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art  
15 have been motivated to administer the EPA composition of the claimed invention to very high  
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a  
17 reasonable expectation of success in achieving the claimed invention.

18  
19 (g) Defendants Have Not Shown that Claim 9 of the  
20 '399 Patent Would Have Been Obvious

21  
22 \_\_\_\_\_  
23 <sup>2269</sup> Defendants' Contentions at 236.

24 <sup>2270</sup> ATP-III at 3170; Bays 2008 I at 395.

<sup>2271</sup> Kwiterovich in Kwiterovich at 4.

1 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
2 Section V.D.3. Because Defendants have not shown the obviousness of the Independent Claim  
3 by clear and convincing evidence, they also have not adequately proven the obviousness of  
4 Claim 9.

5 Defendants contend that it would have been obvious to use the claimed composition to  
6 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.  
7 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
8 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
9 combination of claim elements were all present in the prior art references that would have been  
10 combined by a person of ordinary skill in the art to produce the claimed invention with a  
11 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
12 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
13 element out of the claim. Although convenient and expedient, Defendants' approach does not  
14 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
15 obviousness.

16 Defendants do not identify any combination of references. Because Defendants do not  
17 identify any combination of references, they necessarily fail to offer any evidence that a person  
18 of skill in the art would be motivated to combine those references in order to achieve the  
19 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of  
20 ordinary skill would have been motivated to combine the elements.<sup>2272</sup> As such, Defendants fail  
21

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22 <sup>2272</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 to demonstrate that there was no motivation to combine the references to achieve the claimed  
2 invention.

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. Defendants make conclusory statements without providing any  
7 support. What is more, Defendants do not even discuss the reasonable expectation of reducing  
8 non-HDL-C and VLDL-C levels. As such, Defendants fail to demonstrate reasonable  
9 expectation of success of reducing non-HDL-C and VLDL-C levels using the claimed methods.

10 **4. The '399 Patent is Not Invalid Under § 112**

11 a) Defendants Have Not Demonstrated that the Claims of the '399  
12 Patent Are Invalid for Indefiniteness

13 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]  
14 the subject matter which the applicant regards as his invention.”<sup>2273</sup> Patent claims are valid in  
15 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the  
16 art about the scope of the invention” in light of the specification and the prosecution history.<sup>2274</sup>  
17 The Supreme Court has recognized that “absolute precision is unattainable” in claim language  
18 and “the certainty which the law requires in patents is not greater than is reasonable.”<sup>2275</sup>

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<sup>2273</sup> Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and  
21 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite  
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions  
23 other than by making conclusory assertions in return. Therefore, Defendants should be precluded from  
24 supplementing their naked assertions with new basis in the course of the litigation.

<sup>2274</sup> *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

<sup>2275</sup> *Id.* at 2129.

1 Defendants allege that a number of terms containing the phrases “about” and  
2 “substantially” are indefinite. Defendants do not provide any reason why these terms are  
3 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,  
4 these terms are routinely used in patent claims, and are not *per se* indefinite.<sup>2276</sup> In particular,  
5 courts have held repeatedly that claims that contain the words “about” and “substantially” are not  
6 indefinite.<sup>2277</sup> Here, a person of ordinary skill would understand with reasonable certainty what  
7 is claimed when the claims are read in light of the specification and prosecution history.<sup>2278</sup>  
8 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being  
9 indefinite.

10 Defendants further allege that the terms “4g per day of a pharmaceutical composition  
11 comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” are  
12 indefinite. They contend that, because there is no indication of how much of the pharmaceutical  
13 composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid  
14

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15 <sup>2276</sup> *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms  
16 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the  
17 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.  
18 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the  
19 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d  
20 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe  
21 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish  
22 the claimed subject matter from the prior art, it is not indefinite.”).

23 <sup>2277</sup> *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim  
24 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.  
2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction  
“define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy  
Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration  
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,  
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not  
indefinite).

<sup>2278</sup> *See generally* the ’399 patent and its prosecution history.



1 is present in the composition. This is incorrect. A claim can use a ratio to define amounts of  
2 components in a product, using terms such as “percent by weight.”<sup>2279</sup> In light of the  
3 specification and prosecution history, a person of ordinary skill would understand with  
4 reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the  
5 recited pharmaceutical composition in relation to all fatty acids present.<sup>2280</sup> Therefore, these  
6 terms are not indefinite and do not render the claims indefinite.

7 Defendants further allege that the term “who have not received . . . a concurrent lipid  
8 altering therapy” is indefinite. Defendants provide no basis for this allegation. In light of the  
9 specification and the prosecution history, however, a person of ordinary skill in the art would  
10 understand with reasonable certainty the scope of a “concurrent lipid altering therapy.”<sup>2281</sup> For  
11 example, it was known that Lovaza was prescribed along with statin. Therefore, the phrase  
12 “concurrent lipid altering therapy” does not render the claim indefinite.

13 Defendants further contend that the metes and bounds of the phrase “without  
14 substantially increasing LDL-C” are unclear. Defendants do not provide the basis for the  
15 assertion other than stating that it is unclear and the specification does not clarify its meaning.  
16 As discussed above, use of the phrase “substantially” does not render a claim *per se* indefinite.  
17 In light of the specification and the prosecution history, a person of ordinary skill in the art  
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20 <sup>2279</sup> *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at \*5–6 (D.N.J.  
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a  
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at \*10 (E.D. Tex. Apr. 27,  
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total  
volume of the solution, with this ratio expressed as a percentage”).

23 <sup>2280</sup> See generally the '399 patent and its prosecution history.

24 <sup>2281</sup> See generally the '399 patent and its prosecution history.

1 would know with reasonable certainty the scope of the term “without substantially increasing  
2 LDL-C” and therefore does not render the claims indefinite.<sup>2282</sup>

3 Defendants allege that Claims 1 and 2 are “directly contradictory with respect to  
4 administration or lack thereof to the second group of subjects.” A person of ordinary skill in the  
5 art would understand that Claim 2 discloses “wherein the pharmaceutical composition is  
6 administered to members of the group of subjects 1 to 4 times per day.” This is particularly true  
7 in this case, a person of ordinary skill would understand that the second group of subjects would  
8 *not* be administered the pharmaceutical composition, as required by independent claim 1. Also,  
9 the district court can retroactively correct certain errors in a patent’s claims if “(1) the correction  
10 is not subject to reasonable debate based on consideration of the claim language and the  
11 specification and (2) the prosecution history does not suggest a different interpretation of the  
12 claims.”<sup>2283</sup> In this case, any correction would be directed to an element that is not subject to  
13 reasonable debate and the prosecution history and specification do not suggest a contrary  
14 interpretation.

15 Defendants also allege that it is impossible to ascertain the metes and bounds of “the  
16 second group of subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500  
17 mg/dl.” A person of ordinary skill, however, would understand the metes and bounds of the term  
18 in light of the specification and the prosecution history.<sup>2284</sup> Moreover, the method of comparing  
19 a second group of subjects, such as a placebo controlled, randomized, double blind study, would  
20

21 \_\_\_\_\_  
<sup>2282</sup> See generally the '399 patent and its prosecution history.

22 <sup>2283</sup> *Novo Indus., L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354, 1357 (Fed. Cir. 2003). These “determinations  
23 must be made from the point of view of one skilled in the art.” *Ultimax Cement Mfg. v. CTS Cement Mfg.*, 587 F.3d  
1339, 1353 (Fed. Cir. 2009).

24 <sup>2284</sup> See generally the '399 patent and its prosecution history.

1 have been known to a person of ordinary skill at the time of the invention. Therefore, the term  
2 does not render the claims indefinite.

3 Finally, Defendants contend that the asserted claims improperly mix methods and  
4 formulations because Plaintiffs' assertion of contributory infringement apparently suggests that  
5 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness  
6 analysis is based on what the claim language informs a person of ordinary skill in the art in light  
7 of the specification and the prosecution history. Defendants do not identify any actual claim  
8 language that mixes methods and formulations. Moreover, contributory infringement may be  
9 asserted and proven when a party sells "a material or apparatus for use in *practicing a patented*  
10 *process . . . knowing the same to be especially made or especially adapted for use in an*  
11 *infringement of such patent.*"<sup>2285</sup> Plaintiffs assert that Defendants' ANDA products will be used  
12 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound  
13 itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are  
14 mistaken and the '399 patent claims are not indefinite for improperly mixing methods and  
15 formulations.

16 b) Defendants Have Not Demonstrated that the Claims of the '399  
17 Patent Are Invalid for Insufficient Written Description

18 The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a  
19 written description of the invention." This requires that the specification "reasonably convey"  
20 that the applicant "invented" or "had possession" of the claimed subject matter when the  
21  
22

23 \_\_\_\_\_  
24 <sup>2285</sup> 35 U.S.C. § 271(c) (emphasis added).

1 application was filed.<sup>2286</sup> Support need not be literal<sup>2287</sup>—it may be implicit<sup>2288</sup> or inherent<sup>2289</sup> in  
2 the disclosure. In addition, it is unnecessary to include information that is already known or  
3 available to persons of ordinary skill.<sup>2290</sup>

4 Defendants make three arguments regarding the written description requirement. First,  
5 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack  
6 written description. This is incorrect. The specification of asserted patents literally discloses the  
7 claimed invention.<sup>2291</sup> Moreover, the recited baseline TG levels of the claimed invention appear  
8 in the original claims of the application to which the asserted patent claims priority. Thus, there  
9 is a strong presumption that the claimed invention is adequately described.<sup>2292</sup> Defendants do  
10 not and cannot rebut this presumption. Specifically, the patient population is originally claimed  
11 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500  
12 mg/dl.”<sup>2293</sup> The asserted claims recite the same patient population. Defendants do not contend  
13 that the patient population of the asserted claims is not literally described by the specification  
14

15 <sup>2286</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

16 <sup>2287</sup> *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d  
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

17 <sup>2288</sup> *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866  
F.2d at 424–25.

18 <sup>2289</sup> *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

19 <sup>2290</sup> *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,  
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

20 <sup>2291</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
21 *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
legal foundation for claiming that species.”).

22 <sup>2292</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
23 a description of the invention defined by the claims”).

24 <sup>2293</sup> See U.S. Provisional Application No. 61/151,291.

1 and in the original claims of the application to which the asserted patent claims priority. In fact,  
2 the specification and the provisional patent application claims at the time of filing described  
3 these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the  
4 claimed invention has not been described with sufficient particularity such that one skilled in the  
5 art would recognize that the applicant had possession of the claimed invention.

6 Second, Defendants contend that “a person of skill in the art would not understand that  
7 the inventor was in possession of a method incorporating [] specific dosages and quantities.”  
8 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the  
9 dosages and quantities of the claimed methods.<sup>2294</sup> Moreover, the dosages and quantities of the  
10 method appear in the claims, as originally filed. Thus, there is a strong presumption that the  
11 claimed invention is adequately described.<sup>2295</sup> Defendants do not and cannot rebut this  
12 presumption. For example, the dosage of the composition was originally claimed as “about 1 g  
13 to about 4g.”<sup>2296</sup> The asserted claims recite “4 g.” Defendants do not contend that dosages and  
14 quantities of the asserted claims are not literally described by the specification and in the original  
15 claims. In fact, the specification and the provisional patent application claims, at the time of  
16 filing, described these limitations. Therefore, Defendants have failed to explain whether and  
17 how an aspect of the claimed invention has not been described with sufficient particularity such  
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20 <sup>2294</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
22 legal foundation for claiming that species.”).

23 <sup>2295</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

<sup>2296</sup> See U.S. Provisional Application No. 61/151,291.

1 that one skilled in the art would recognize that the applicant had possession of the claimed  
2 invention.

3 Third, Defendants contend that “a person of skill in the art would not understand that the  
4 inventor was in possession of a method comprising a comparison against a second group of  
5 subjects.” Although this allegation does not appear to implicate written description, the  
6 specification describes such a comparison. Therefore, a person of ordinary skill would have  
7 understood that the inventor was in possession of a method comprising administration of a  
8 composition with the recited properties, based on a specific comparison of a subject or a  
9 population against a second group of subjects.

10 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,<sup>2297</sup> the court  
11 elaborated that “possession” means possession as evidenced by disclosure. In this case, the  
12 specification of asserted patents literally disclose the claimed invention in the specification and  
13 the claims as originally filed. Thus, an examination of the four corners of the specification from  
14 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the  
15 asserted patents were in possession of the claimed invention.

16 Defendants conclude by alleging that the specification does not describe anything more  
17 than what is obvious, and thus does not provide adequate support for any nonobvious claim.  
18 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the  
19 specification; nonobviousness can be supported by post-filing date evidence for example.<sup>2298</sup>  
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21 <sup>2297</sup> *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

22 <sup>2298</sup> See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)  
23 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is  
24 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those  
characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,  
1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained

1 Written description requires only that the specification reasonably conveys that the applicant had  
2 possession of the claimed subject matter when the application was filed. Therefore, whether the  
3 claims are obvious has no bearing on the adequacy of written description.

4 c) Defendants Have Not Demonstrated that the Claims of the '399  
5 Patent Are Invalid for Lack of Enablement

6 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person  
7 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would  
8 require undue experimentation for a person of ordinary skill to make or use the invention.

9 Factors that may be considered include the quantity of experimentation necessary, the amount of  
10 direction or guidance presented, the presence or absence of working examples, the nature of the  
11 invention, the state of the prior art, the relative skill of those in the art, the predictability or  
12 unpredictability of the art, and the breadth of the claims.<sup>2299</sup> The enablement requirement is  
13 separate and distinct from the written description requirement,<sup>2300</sup> and as such a claim does not  
14 require descriptive support in the disclosure as originally filed for it to be enabled.<sup>2301</sup>

15 Defendants make two specific arguments regarding the enablement requirement. First,  
16 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of  
17 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the  
18 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary  
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21 after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.  
22 2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full  
range of an invention is not always achieved at the time of filing the patent application.”).

23 <sup>2299</sup> See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

24 <sup>2300</sup> *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

<sup>2301</sup> MPEP § 2164.

1 skill would be able to determine the amounts of the components in the pharmaceutical  
2 composition without any experimentation, much less undue experimentation.

3 Second, Defendants contend that it would take undue experimentation to obtain the  
4 claimed required results listed in the full scope of the patent claims, including the claimed lipid  
5 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed  
6 method and certainly not undue experimentation. Administration of a recited amount of a recited  
7 composition, for a recited duration, to a specific, recited patient population produces the recited  
8 results. No additional experimentation is required, and Defendants do not explain their  
9 allegation that undue experimentation would be required. Defendants also do not contend that  
10 following the claimed method (each recited element) does not produce the recited results. The  
11 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly  
12 demonstrate that administration of EPA of the recited composition, when administered to  
13 patients with very high TG levels for at least 12 weeks, as specified, produces the recited  
14 results.<sup>2302</sup> Therefore, the claims are not invalid for lack of enablement.

15 Defendants conclude by alleging that the specification does not enable anything more  
16 than what is obvious over the prior art or was known to a person of skill in the art. First,  
17 Defendants do not cite any case or present a legal theory to support this assertion. As such, they  
18 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be  
19 precluded in the future from raising any new legal theory to support this assertion. Moreover,  
20 while the '399 patent's specification enables a person of ordinary skill to obtain the claimed  
21 limitations without undue experiment, the claimed limitations would not have been obvious to a  
22 person of ordinary skill, as discussed in Section V.B.3. Furthermore, Plaintiffs have initiated

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24 <sup>2302</sup> See VASCEPA Prescribing Information at Table 2.



1 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its  
2 claimed methods.<sup>2303, 2304</sup> Therefore, a person of ordinary skill would have concluded that the  
3 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

4 E. **The '677 Patent**

5 1. **The '677 Patent Claims Eligible Subject Matter Under § 101**

6 Defendants' allegation that the asserted claims of the '677 patent relate to ineligible  
7 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*  
8 case under Section 101 or provide a legal or factual basis to support their allegations.

9 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local  
10 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be  
11 provided.<sup>2305</sup> The bare assertion of invalidity under Section 101 without providing the grounds  
12 for such an allegation and examining the elements of the asserted claims of the '677 patent does  
13 not meet this requirement and thwarts the purpose of the Rules.<sup>2306</sup>

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16 <sup>2303</sup> *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any  
17 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical  
18 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that  
19 the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

20 <sup>2304</sup> See May 16, 2011 Bays Declaration at Appendix B.

21 <sup>2305</sup> See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all  
22 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed  
23 statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

24 <sup>2306</sup> Nor does the preceding paragraph, which provides only a purported summary of the claims of the '677 patent, or  
subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the  
grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,  
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent  
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide  
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those  
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

1 The inquiry under Section 101 involves a two-step test: first, a court must determine  
2 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical  
3 phenomenon, or abstract idea.<sup>2307</sup> Second, even if the claim is directed to one of these concepts,  
4 it still may be patent eligible and the court must determine what else is part of the claim.<sup>2308</sup>

5 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*  
6 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of  
7 the '677 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]  
8 conventional” steps, and the only novel element related to administering the proper dosage based  
9 on a natural law observation.<sup>2309</sup> However, the claims merely recited this natural law without  
10 reciting any novel application of it.<sup>2310</sup> The Court found that providing protection to such  
11 claims would result in pre-empting “a broad range of potential uses” and excluding others from  
12 using “the basic tools of scientific and technical work.”<sup>2311</sup> A method of treatment claim,  
13 specifying the subjects, dosage levels, composition, and time course does not raise the concerns  
14 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent  
15 protection.<sup>2312</sup>

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17 <sup>2307</sup> *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at  
18 issue are directed to one of those patent-ineligible concepts.”).

18 <sup>2308</sup> *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

19 <sup>2309</sup> *Mayo*, 132 S. Ct. at 1294.

20 <sup>2310</sup> *Id.* at 1301.

20 <sup>2311</sup> *Id.*

21 <sup>2312</sup> *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way  
22 of using an existing drug); see also *Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability  
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula  
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d  
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent  
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

1 Defendants suggest that the recited EPA composition of each asserted claim is a naturally  
2 occurring substance. It is not. Even references contained within Defendants’ own contentions  
3 make clear that EPA of the requisite purity and characteristics is not found in nature.<sup>2313</sup> As  
4 expressed by the patents cited in Defendants’ contentions and well-established precedent, for  
5 decades it has been accepted that compositions isolated from nature or purified beyond their  
6 natural state are patent-eligible.<sup>2314</sup> Moreover, Defendants’ assertions are immaterial to a Section  
7 101 defense because method of treatment claims like the ones asserted in this case are patent  
8 eligible even if they are directed to administration of a naturally occurring substance.<sup>2315</sup>

9 To the extent Defendants are arguing that a law of nature both underlies the claims and  
10 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the  
11 claimed effects are the natural result of ingesting a naturally-occurring substance.”<sup>2316</sup> Since the  
12 composition that is the subject of the claims is not naturally occurring, Defendants appear to  
13 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states  
14 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad  
15 characterization of laws of nature.<sup>2317</sup> To say that the claims of the ’677 patent claim a law of  
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17 <sup>2313</sup> See, e.g., U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative  
18 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, e.g., at 26–27).

19 <sup>2314</sup> See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394  
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

20 <sup>2315</sup> *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

21 <sup>2316</sup> See Defendants’ Joint Invalidity Contentions at 299.

22 <sup>2317</sup> See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes  
23 to achieve a desired outcome . . . . That one way of describing the process is to describe the natural ability of the  
24 subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we  
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability  
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to  
aspirin).”).

1 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode  
2 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to  
3 underlying principles of nature” that would “make all inventions unpatentable.”<sup>2318</sup> Indeed, even  
4 those concerned about the implications of *Mayo* on future patents were focused on diagnostic  
5 claims not treatment claims of the type that *Mayo* stated were typical and patentable.<sup>2319</sup>

6 Even if there is some underlying law of nature in the asserted claims, the subject matter  
7 of the '677 patent remains eligible for protection under Section 101. As articulated by *Mayo* and  
8 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to  
9 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to  
10 foreclose from others the use of that equation in conjunction with all of the other steps in their  
11 claimed process.’”<sup>2320</sup> As discussed above, the asserted claims of the '677 patent contain a  
12 novel, unconventional, and specific method of treatment comprising a particularized application  
13 of a nonnaturally occurring substance and does not preempt the use of a law of nature.<sup>2321</sup>

14 Defendants also argue that any argument by Amarin in response to Defendants’ § 112  
15 arguments are further evidence of invalidity under § 101. This argument is without merit. The  
16 claims are enabled and written description is satisfied for the reasons discussed below. In  
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<sup>2318</sup> See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

20 <sup>2319</sup> See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying  
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,  
particularly in the area of diagnostic research.”).

22 <sup>2320</sup> See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 <sup>2321</sup> See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at \*4 (C.D. Cal. July 24, 2012)  
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was  
“just one step in the whole process” claimed by the invention).

1 addition, as discussed above, the asserted claims are not merely a naturally-occurring  
2 phenomena, and thus satisfy the requirements of § 101.

3 **2. The Asserted Claims of the ‘677 Patent Are Not Anticipated by WO**  
4 **‘118**

5 To anticipate, a single prior art reference must sufficiently describe a claimed invention  
6 so that the public is in “possession” of that invention.<sup>2322</sup> Therefore, to anticipate, a reference  
7 must set forth every element of the claim, either expressly or inherently, in as complete detail as  
8 is contained in the claim.<sup>2323</sup> The claim elements must also be “arranged” in the prior art  
9 reference, just as they are in the claim,<sup>2324</sup> rather than as “multiple, distinct teachings that the  
10 artisan might somehow combine to achieve the claimed invention.”<sup>2325</sup> In addition, public  
11 “possession” requires that the prior art enable a person of ordinary skill to make and use the  
12 invention without undue experimentation.<sup>2326</sup> Factors that may be included in this analysis  
13 include the quantity of experimentation necessary, the amount of direction or guidance  
14 presented, the presence or absence of working examples, the nature of the invention, the state of  
15 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,

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<sup>2322</sup> *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

20 <sup>2323</sup> *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.  
21 Cir. 1989).

22 <sup>2324</sup> *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

23 <sup>2325</sup> *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587  
24 (C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

<sup>2326</sup> *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,  
Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

1 and the breadth of the claims.<sup>2327</sup> This inquiry is objective, and thus evidence of undue  
2 experimentation need not be prior art.<sup>2328</sup>

3 Defendants assert that Claims 1-9 of the '677 Patent are anticipated by the WO '118  
4 reference.<sup>2329</sup>

5 A element-by-element analysis, identifying each element of each asserted claim that is  
6 absent from WO '118, is provided below. The contentions below are incorporated by reference  
7 into Exhibit E, and vice-versa. WO '118 does not anticipate the claims of the '677 patent  
8 because it does not describe, properly arrange, or enable the '677 patent claims.

9 a) WO '118 Does Not Teach Every Element of the Claims of the  
10 '677 Patent

11 (1) WO '118 Does Not Describe the Claimed Lipid Effects

12 It is well established that, for a prior art reference to anticipate, “every element of the  
13 claimed invention must be identically shown in a single reference.”<sup>2330</sup> Moreover, the elements  
14 of the claimed invention must have “strict identity” with the elements of the reference; “minimal  
15 and obvious” differences are sufficient to prevent anticipation.<sup>2331</sup> Here, WO '118 entirely fails  
16 to disclose the following elements of Claim 1 of the '677 Patent: *to effect a reduction in*  
17 *triglycerides without substantially increasing LDL-C compared to placebo control.* Defendants

18 <sup>2327</sup> *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

19 <sup>2328</sup> *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999  
20 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.  
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822  
F.2d 1074, 1078 (Fed. Cir. 1987).

21 <sup>2329</sup> References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs  
reserve their right to obtain a certified translation of WO '118.

22 <sup>2330</sup> *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*  
23 *Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

24 <sup>2331</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth  
2 any basis for concluding that WO '118 teaches this element.<sup>2332</sup> Indeed, Defendants could not  
3 set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

4       Instead, Defendants argue that these elements express the intended result of a method that  
5 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth  
6 below, WO '118 fails to disclose each element of the independent claim of the '677 Patent, either  
7 expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants  
8 also argue that these elements represent inherent, natural properties of EPA, and are entitled to  
9 no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation  
10 and claim construction. Further, while Defendants argue that the inherent properties are  
11 exemplified in the prior art, they fail to identify even a single prior art reference that makes such  
12 a disclosure. Defendants cannot point to a single, specific prior art reference because the  
13 claimed pharmaceutical composition has never been administered in the manner claimed to the  
14 claimed patient population. Also, these elements are positively recited in the body of the claim  
15 and therefore cannot be construed as a non-limiting preamble and must be given patentable  
16 weight.

17       Further, Defendants entirely fail to prove that inherently discloses the claimed lipid  
18 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
19 inherently anticipate as a matter of law.”<sup>2333</sup> “[A]nticipation by inherent disclosure is appropriate  
20 only when the reference discloses prior art that must *necessarily* include the unstated

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23 <sup>2332</sup> Defendants’ Invalidation Contentions at 202-204.

24 <sup>2333</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

1 limitation.”<sup>2334</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
2 possibly present’ in the prior art.”<sup>2335</sup> WO ‘118 fails to provide any data related to the lipid  
3 effects of the disclosed invention on patients described in the publication. Therefore, Defendants  
4 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets  
5 the elements of the independent claim every time it is administered.

6 Defendants fail to demonstrate that administration of the claimed EPA compositions  
7 “necessarily” yields the claimed lipid effects. For example, one study cited by Defendants  
8 suggests that EPA administration may increase LDL-C.<sup>2336</sup> Rambjor is a clinical study which  
9 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA  
10 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a  
11 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*  
12 decrease TG without increasing LDL-C *every time it is administered*.

13 Therefore, WO ‘118 cannot anticipate the independent claim of the ‘677 patent. Because  
14 the dependent claims include all of the claim elements of the independent claim, WO’ 118  
15 cannot anticipate any of the dependent claims as well.

16 (2) WO ‘118 Does Not Disclose Methods of Treating The  
17 Claimed Patient Population

18 In addition, WO ‘118 fails to disclose or suggest the claimed pharmaceutical composition  
19 be administered in the manner claimed to the claimed patient population. Defendants attempt to  
20 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is  
21 the introductory clause of a patent claim and includes everything from the beginning of the claim

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<sup>2334</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 <sup>2335</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 <sup>2336</sup> *See, e.g., Rambjor*.



1 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the  
2 preamble.

3 A claim preamble has patentable weight if, “when read in the context of the entire claim,  
4 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,  
5 and vitality’ to the claim.”<sup>2337</sup> Additionally, the preamble constitutes a claim element when the  
6 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and  
7 claim body to define the claimed limitation.”<sup>2338</sup>

8 The preamble of the asserted claims is limiting for several reasons. The term “subject” in  
9 the preamble of the independent claim defines and provides antecedent basis for the “subject”  
10 recited in the body of the claims. When reading the claim, one must rely on both the preamble  
11 and the claim body to define the claimed invention.

12 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is  
13 properly construed as a limitation of the claim itself.”<sup>2339</sup> The recitation of a “method of  
14 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing  
15 triglycerides in the body of the claim and emphasizes the intentional purpose for which the  
16 method must be performed - to reduce triglycerides.

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<sup>2337</sup> *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 <sup>2338</sup> *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 <sup>2339</sup> *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*  
23 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases  
24 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a  
necessary and defining aspect of the invention, specifically its portability,” and because the specification and  
prosecution history “emphasize this feature of the invention”).

1 It is clear that “the claim drafter chose to use both the preamble and the body of the claim  
2 to define the subject matter of the claimed invention.”<sup>2340</sup> Thus, the entire preamble in the  
3 independent claim of the ‘677 must contain patentable weight.

4 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.  
5 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be  
6 administered in the manner claimed to the claimed patient population.

7 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,  
8 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**  
9 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the  
10 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence  
11 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and  
12 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden  
13 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest  
14 angina and exercise-induced angina, and destabilization of the angina.”<sup>2341</sup> The invention of WO  
15 ‘118 is intended to be administered to any person in need of prevention of the occurrence of  
16 cardiovascular events, who are typically hypercholesterolemia patients.<sup>2342</sup> WO ‘118 does not  
17 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot  
18 anticipate the independent claim.

19 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail  
20 to prove that these elements of the claimed invention have “strict identity” with the elements of  
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22 <sup>2340</sup> *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

23 <sup>2341</sup> WO ‘118 at 12.

24 <sup>2342</sup> *Id.*

1 the reference.<sup>2343</sup> WO '118 fails to anticipate this claim element because the broad disclosure  
2 fails to anticipate the narrow claimed range, and the specific patient population defined in the  
3 claims is an essential part of the claimed invention.

4 There is no evidence in that subject as described in the claims were ever treated. In fact,  
5 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the  
6 definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of  
7 the subject as described in the claims. It does not. Defendants' argument rests on the definition  
8 in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150  
9 mg/dL." WO '118's definition is not tied to a specific subject and there are no working  
10 examples, data or other reference in WO '118 indicating that any subject with fasting TG levels  
11 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any  
12 EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as  
13 evidence that a "person of ordinary skill in the art would have understood that the term  
14 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of  
15 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable  
16 and then merely provides examples of commercially available "soft capsules," such as Omacor.  
17 The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients  
18 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be  
19 used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or  
20 'possibly' meets the claims cannot inherently anticipate as a matter of law."<sup>2344</sup> Therefore,

23 <sup>2343</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 <sup>2344</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

1 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO  
2 '118 meets the claim elements of the independent claim every time it is administered.

3 Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges  
4 claimed by the '677 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500  
5 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between  
6 330 and 450 degrees. The court found that the broader prior art range could not anticipate the  
7 claimed temperature range, “[g]iven the considerable difference between the claimed range and  
8 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the  
9 claimed range with sufficient specificity to anticipate this element of the claim.”<sup>2345</sup> A prior art’s  
10 teaching of a broad genus does not necessarily disclose every species within that genus. The  
11 court explained the slightly overlapping range between the preferred range and claimed range “is  
12 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>2346</sup> and therefore  
13 failed to anticipate the claimed range. Likewise, WO '118’s broad disclosure of  
14 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not  
15 anticipate the subject as described in the claims because it fails to described the claimed TG  
16 range with sufficient specificity.

17 The court in *Atofina* ruled on an additional question of anticipation that also involved a  
18 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as  
19 compared to the patent’s claimed range of 0.1 to 5.0 percent.<sup>2347</sup> The court explained that  
20 “although there is a slight overlap, no reasonable fact finder could determine that this overlap  
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22 <sup>2345</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

23 <sup>2346</sup> *Atofina*, 441 F.3d at 1000.

24 <sup>2347</sup> *Id.*

1 describes the entire claimed range with sufficient specificity to anticipate this limitation of the  
2 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”<sup>2348</sup> Similarly,  
3 although there may be overlap between the definition of hypertriglyceridemia taught by WO  
4 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not  
5 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500  
6 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of  
7 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels  
8 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic  
9 events as the primary clinical objective),<sup>2349</sup> WO ‘118, therefore, does not expressly disclose the  
10 specific patient population that is an essential element of the claims of the asserted patents.  
11 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

12           The treatment of a patient with elevated TG levels varies depending on their serum  
13 triglyceride levels. Identification of the patient population with very high TG levels (at least 500  
14 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,  
15 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment  
16 of lipid disorders.<sup>2350</sup> The ATP-III divided hypertriglyceridemia patients into three classes based  
17 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),  
18 and very-high TGs ( $\geq 500$  mg/dL)—and recommended substantially different treatment  
19 strategies for patients depending on classification.<sup>2351</sup> For the borderline-high and high TG

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21 <sup>2348</sup> *Id.*

22 <sup>2349</sup> *See* Section III.

23 <sup>2350</sup> *Id.*

24 <sup>2351</sup> ATP III at 3335; *See also* Section III.

1 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.<sup>2352</sup>  
2 Accordingly, in these populations, physicians focused on lowering LDL-C.<sup>2353</sup> In this patient  
3 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.  
4 In contrast, the primary goal for very-high TG patients ( $\geq 500$  mg/dL) was to reduce the risk of  
5 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated  
6 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary  
7 treatment goal.<sup>2354</sup> Therefore, as evidenced by the ATP-III, patients with very-high TG levels  
8 were considered fundamentally different from patients with borderline-high or high TGs from a  
9 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

10 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride  
11 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In  
12 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at  
13 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular  
14 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).  
15 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels  
16 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by  
17 decreasing triglycerides), as required by the independent claims of the asserted patents, and  
18 therefore cannot anticipate the independent claim of the ‘677 Patent.

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<sup>2352</sup> *Id.*

23 <sup>2353</sup> *Id.*

24 <sup>2354</sup> *Id.*

1 (3) WO '118 Does Not Describe the Claimed Pharmaceutical  
2 Composition or its Specific Administration

3 WO '118 further does not anticipate the claims of the '677 patent because it does not  
4 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as  
5 claimed, it cannot anticipate oral administration to the claimed "subject."

6 WO '118 additionally cannot anticipate the claims of the '677 patent because it does not  
7 disclose administering the pharmaceutical composition at a dose of about 4g per day.  
8 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is  
9 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which  
10 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more  
11 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8  
12 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is  
13 not particularly limited as long as the intended effect, preventing the occurrence of  
14 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose  
15 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be  
16 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no  
17 working examples, data or other reference in WO '118 indicating that any subject (much less  
18 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the  
19 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

20 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of  
21 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The  
22 court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic  
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1 range of 330 to 450 °C,”<sup>2355</sup> and therefore failed to anticipate the claimed range. The court in  
2 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate  
3 the patent’s claimed range of 0.1 to 5.0 percent.<sup>2356</sup> The court explained that “although there is a  
4 slight overlap, no reasonable fact finder could determine that this overlap describes the entire  
5 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are  
6 different, not the same. . . . Thus, there is no anticipation.”<sup>2357</sup> Similarly, although there may be  
7 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘677  
8 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range  
9 claimed by the ‘677 patent does not fall within WO ‘118’s preferred range. Defendants  
10 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,  
11 the example indicates that up to 900 mg of the EPA composition could be used three times per  
12 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘677  
13 patent and cannot anticipate the independent claim of the ‘677 Patent.

14 WO ‘118 further does not anticipate the claims of the ‘677 patent because it does not  
15 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a  
16 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.  
17 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high  
18 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and  
19 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or  
20 higher, and still more preferably 96.5% by weight or higher.”<sup>2358</sup> Therefore, WO ‘118 discloses

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22 <sup>2355</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>2356</sup> *Id.*

23 <sup>2357</sup> *Id.*

24 <sup>2358</sup> WO ‘118 at 22.



1 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total  
2 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed  
3 generic range for the EPA composition in the claimed pharmaceutical composition.

4 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the  
5 . . . range claimed in the” patent is insufficient for anticipation.<sup>2359</sup> In *Atofina*, the prior art  
6 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a  
7 range between 330 and 450 degrees. The court explained that this slight overlap “is not  
8 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>2360</sup> and therefore failed  
9 to anticipate the claimed range.<sup>2361</sup> The court in *Atofina* also found that a prior art disclosure of a  
10 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0  
11 percent.<sup>2362</sup> The court explained that “although there is a slight overlap, no reasonable fact finder  
12 could determine that this overlap describes the entire claimed range with sufficient specificity to  
13 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no  
14 anticipation.”<sup>2363</sup>

15 Similarly, although there may be some overlap between the E-EPA content disclosed by  
16 WO ‘118 and the ranges claimed by the ‘677 patent, WO ‘118 does not specifically highlight the  
17 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a  
18 critical factor of the invention disclosed in the ‘677 patent. Therefore, WO ‘118’s broad  
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21 <sup>2359</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

22 <sup>2360</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>2361</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>2362</sup> *Id.*

24 <sup>2363</sup> *Id.*

1 disclosure of the E-EPA content in its invention does not describe the claimed range with  
2 sufficient specificity and cannot anticipate the independent claim of the '677 patent.

3 WO '118 is additionally insufficient for anticipation because it does not expressly  
4 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118  
5 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is  
6 DHA-E."<sup>2364</sup> The disclosure goes on to state that the composition of the invention is preferably  
7 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed  
8 pharmaceutical composition is a critical factor of the invention disclosed in the '677 patent.

9 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed  
10 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.  
11 There is no express teaching or guidance directing the person of ordinary skill in the art to the  
12 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no  
13 difference between the use of EPA or DHA in its invention, cannot anticipate the independent  
14 claim of the '677 patent.

15 Defendants contend that Plaintiffs are estopped from arguing there is any material  
16 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants  
17 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing  
18 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is  
19 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and  
20 Defendants have cited no authority to support their position suggesting the contrary. The  
21 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases  
22 and are not co-extensive. Accordingly, plaintiffs are not estopped.

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<sup>2364</sup> WO '118 at 22.

1 In the same paragraph containing their allegation of estoppel, Defendants also quote from  
2 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their  
3 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these  
4 statements form the basis for any theory of estoppel. To the extent that Defendants quote  
5 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The  
6 quoted statements do not identify any recited claim element, including the specific  
7 pharmaceutical composition, the recited patient population, administration in the manner  
8 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from  
9 the quoted statements.

10 (4) WO '118 Does Not Describe the Dependent Claims

11 Defendants fail to address any of the claim elements of the dependent claims.  
12 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail  
13 to set forth any meaningful basis for concluding that WO '118 teaches these elements.  
14 Defendants further argue that "aspects of the claims relating to effects that are to be achieved by  
15 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to  
16 no patentable weight." To the extent the recited claim elements relate to the administration step,  
17 the dosage form or characteristics of the treated subject and the specific effect produced by the  
18 claimed method, Defendants' contentions that the claim limitations are inherent properties of  
19 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO  
20 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.  
21 Defendants have not met the burden to establish anticipation with the naked assertion that the  
22 effects are inherent, natural properties of EPA.

23 Further, Defendants entirely fail to prove that inherently discloses the recited claim  
24 limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot

1 inherently anticipate as a matter of law.”<sup>2365</sup> “[A]nticipation by inherent disclosure is appropriate  
2 only when the reference discloses prior art that must *necessarily* include the unstated  
3 limitation.”<sup>2366</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
4 possibly present’ in the prior art.”<sup>2367</sup> Defendants fail to show that WO ‘118 “*necessarily*” meets  
5 the recited claim elements relating to the administration step, the dosage form or characteristics  
6 of the treated subject and the specific effect produced by the claimed method *every time*. WO  
7 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total  
8 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in  
9 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,  
10 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and  
11 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim  
12 elements.

### 13 3. The Claims of the ‘677 Patent Would Not Have Been Obvious In 14 Light of the Asserted References

15 Defendants identify 77 separate references that it asserts somehow render the claims of  
16 the ‘677 Patent obvious.<sup>2368</sup> Defendants fail to demonstrate by clear and convincing evidence  
17 that any of these references, alone or in combination, would render obvious any claims of the  
18 ‘677 Patent. Defendants’ arguments rely on hindsight by impermissibly using the blueprint of  
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21 <sup>2365</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

22 <sup>2366</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 <sup>2367</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 <sup>2368</sup> Defendants’ Joint Invalidity Contentions at 13-25.

1 the '677 Patent itself to guide its combination of references.<sup>2369</sup> Defendants chart a laundry list  
2 of 77 separate references, without explanation. Defendants' disclosures do not comply with  
3 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly  
4 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs  
5 cannot respond to undisclosed combinations and arguments.<sup>2370</sup>

6 Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions,  
7 Plaintiffs have discerned and will specifically respond to the following alleged prior art  
8 combinations:

- 9 • 1) “. . .the asserted claims of the '677 patent would have been obvious over the  
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
11 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in  
12 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori  
13 2000.”
- 14 • 2) “. . .the asserted claims of the '677 patent would have been obvious over the  
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
16 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,  
17 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori  
18 2000 and/or Maki.”
- 19 • 3) “. . .the asserted claims of the '677 patent would have been obvious over the  
20 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
21 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view  
22 of Satoh or Shinozaki in further view of Contacos.”
- 23 • 4) “. . . the asserted claims of the '677 patent would have been obvious over WO '118  
24 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the  
Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”

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20 <sup>2369</sup> *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention  
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is  
obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 <sup>2370</sup> This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,  
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for  
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the  
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that  
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to  
rely on undisclosed or insufficiently disclosed references or argument.

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- 2 • 5) “. . . the asserted claims of the ’677 patent would have been obvious over WO
  - 3 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
  - 4 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
  - 5 further in view of Katayama, Matsuzawa and/or Takaku.”

6 A patent claim is invalid “if the differences between the subject matter sought to be

7 patented and the prior art are such that the subject matter as a whole would have been obvious at

8 the time the invention was made to a person having ordinary skill in the art.”<sup>2371</sup> Obviousness is

9 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,

10 (2) the scope and content of the prior art, and (3) the differences between the prior art and the

11 claims at issue.<sup>2372</sup>

12 In evaluating obviousness, each prior art reference must be evaluated for all that it

13 teaches, including the portions that would lead away from the claimed invention.<sup>2373</sup> Indeed, any

14 teaching in the art that points away from the claimed invention must be considered.<sup>2374</sup> A

15 reference teaches away if a person of ordinary skill, upon reading the reference, would be

16 discouraged from following the path set out in the reference, or would be led in a direction

17 divergent from the path that was taken by the applicant.<sup>2375</sup> For instance, a reference teaches

18 away if it suggests that the line of development flowing from the reference’s disclosure is

19 unlikely to be productive of the result sought by the applicant.<sup>2376</sup>

20 <sup>2371</sup> 35 U.S.C. § 103(a).

21 <sup>2372</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

22 <sup>2373</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2374</sup> *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

24 <sup>2375</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

<sup>2376</sup> *Id.*

1 In order to find obviousness based on a combination of references, there must be some  
2 rationale for combining the references in the way claimed that is separate and apart from the  
3 hindsight provided by the patented invention itself.<sup>2377</sup> The law prohibits an obviousness  
4 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art  
5 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of  
6 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed  
7 invention.”<sup>2378</sup> “The invention must be viewed not after the blueprint has been drawn by the  
8 inventor, but as it would have been perceived in the state of the art that existed at the time the  
9 invention was made.”<sup>2379</sup>

10 “The determination of obviousness is made with respect to the subject matter as a whole,  
11 not separate pieces of the claim.”<sup>2380</sup> “[A] patent composed of several elements is not proved  
12 obvious merely by demonstrating that each of its elements was, independently, known in the  
13 prior art.”<sup>2381</sup> “This is so because inventions in most, if not all, instances rely upon building  
14 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations  
15 of what, in some sense, is already known.”<sup>2382</sup>

16 Accordingly, it is improper to pick and choose isolated elements from the prior art and  
17 combine them so as to yield the invention<sup>2383</sup> or to modify a prior art reference in a way that

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19 <sup>2377</sup> *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

20 <sup>2378</sup> *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

21 <sup>2379</sup> *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

22 <sup>2380</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

23 <sup>2381</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

24 <sup>2382</sup> *KSR*, 550 U.S. at 418-419.

<sup>2383</sup> *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

1 “would destroy the fundamental characteristics of that reference.”<sup>2384</sup> Moreover, a combination  
2 is not obvious where “it would be impossible to apply these teachings [of the secondary  
3 reference] to the [primary reference] without entirely changing the basic mechanism and  
4 procedure thereof,”<sup>2385</sup> or where the proposed combination requires “material and radical  
5 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the  
6 prior art device.<sup>2386</sup> Furthermore, it is improper “to modify the secondary reference before it is  
7 employed to modify the primary reference” in assessing obviousness.<sup>2387</sup>

8 Further, a party asserting obviousness in view of a combination of prior art disclosures  
9 must show that a person of ordinary skill in the relevant field had an “apparent reason” to  
10 combine the elements in the manner claimed<sup>2388</sup> and “a reasonable expectation of success.”<sup>2389</sup>

11 For chemical compounds, there must have been a reason both to select the prior art  
12 compound “most promising to modify” and to make the necessary changes to arrive at the  
13 claimed compound.<sup>2390</sup> This protects against the use of hindsight to pick through the prior art  
14

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15 <sup>2384</sup> *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

16 <sup>2385</sup> *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

17 <sup>2386</sup> *Id.* at 88.

18 <sup>2387</sup> *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

19 <sup>2388</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 <sup>2389</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

23 <sup>2390</sup> *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–  
24 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*  
*Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).



1 based solely on structural similarity to the claimed compound.<sup>2391</sup> Any assertion of an “apparent  
2 reason” must find a basis in the factual record.<sup>2392</sup>

3 The “reasonable expectation of success” for a chemical compound must be of all of a  
4 claimed compound’s relevant properties,<sup>2393</sup> including those discovered after the patent was filed  
5 or even issued.<sup>2394</sup> “The basic principle behind this rule is straight-forward—that which would  
6 have been surprising to a person of ordinary skill in a particular art would not have been  
7 obvious.”<sup>2395</sup> Any assertion of a “reasonable expectation of success” must find a basis in the  
8 factual record.<sup>2396</sup>

9  
10 <sup>2391</sup> *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at \*14. *Accord In re Vaidyanathan*, 381. 985, 994  
11 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.  
12 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.  
13 2002).

14 <sup>2392</sup> *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions  
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to  
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the  
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at  
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*  
19 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed  
20 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438  
21 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in  
22 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that  
23 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
24 motivated to resolve citalopram in June 1988”).

25 <sup>2393</sup> *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success  
26 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .  
27 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of  
28 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d  
29 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the  
30 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of  
31 pharmacological properties that it possesses.”).

32 <sup>2394</sup> *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at  
33 908.

34 <sup>2395</sup> *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,  
35 such as chemistry, where minor changes in a product or process may yield substantially different results.”).

36 <sup>2396</sup> *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Aptex argues that the district court applied an incorrect  
37 inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were

1 In an obviousness determination, any objective indicia of nonobviousness must be taken  
2 into account.<sup>2397</sup> An objective indicium is any “event[] proved to have actually happened in the  
3 real world” that evidences the nonobvious nature of the invention.<sup>2398</sup> The existence of an  
4 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or  
5 surprising results, expressions of skepticism, industry praise, commercial success, and copying  
6 are classical indicia of nonobviousness.<sup>2399</sup> These factual inquiries “guard against slipping into  
7 use of hindsight,”<sup>2400</sup> and “may often be the most probative and cogent evidence of  
8 nonobviousness.”<sup>2401</sup>

9 Also, as with assertions of anticipation, in order for an invention to be obvious, it must  
10 have been fully “in possession” of the public—which requires that the claimed invention have  
11 been enabled.<sup>2402</sup>

12  
13  
14 unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general  
15 knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955  
16 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.  
17 However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly  
18 expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re*  
19 *May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a  
20 substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”)

21 <sup>2397</sup> *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

22 <sup>2398</sup> *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

23 <sup>2399</sup> *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*  
24 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750  
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

<sup>2400</sup> *Graham*, 383 U.S. at 36.

<sup>2401</sup> *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*  
*Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

<sup>2402</sup> *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for  
obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,  
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for  
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound  
itself is in the possession of the public.”).

1 A element-by-element analysis, identifying each limitation of each asserted claim that is  
2 absent from the prior art, is provided below, and also provided at Exhibit E. The contentions  
3 below are incorporated by reference into Exhibit E, and vice-versa.

4 a) General Overview

5 Defendants fail to provide a single prior art reference that discloses administration of the  
6 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population  
7 ( $\geq 500$  mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,  
8 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying  
9 degrees of purity, in a wide range of doses and administration periods, to subjects who have  
10 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance  
11 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo  
12 controlled studies are considered the “gold standard” of clinical studies. Studies involving the  
13 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot  
14 distinguish between the effect of the placebo from that of the active agent. Studies which  
15 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the  
16 independent effects of EPA and DHA.<sup>2403</sup> Inconsistency in dosages and administration periods  
17 and variations in the administered fatty acid compositions also complicate the interpretation of  
18 the results and limit the application of these studies.

19 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with  
20 very high TGs together with patients with high and borderline high TGs indicates that there is no  
21 medical difference in responsiveness to treatment among the groups of people.”<sup>2404</sup> Defendants  
22

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23 <sup>2403</sup> Mori 2006 at 96.

24 <sup>2404</sup> Defendants’ Joint Invalidity Contentions at 310 (*see* FN 46).

1 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-  
2 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in  
3 patients with high triglycerides ( $\geq 200$  mg/dL and  $< 500$  mg/dL) who were also on statin therapy.  
4 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g  
5 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG  
6 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that  
7 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.<sup>2405</sup> In  
8 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were  
9 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use  
10 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a  
11 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the  
12 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to  
13 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.  
14 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical  
15 difference in responsiveness to treatment between the very-high TG patient population and lower  
16 TG patient populations merely because there was possibly one patient with baseline TG levels of  
17 at least 500 mg/dL.

18 As discussed above in Section III, patients with very-high TG levels were considered  
19 fundamentally different from patients with borderline-high or high TGs from a clinical,  
20 regulatory, and therapeutic perspective.<sup>2406</sup> Clinically, the authoritative guidance to physicians

22 <sup>2405</sup> FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6  
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been  
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline  
TG values < 500 mg/dL).

24 <sup>2406</sup> See Bays Jan. 8, 2012 Decl., ¶ 20.

1 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III  
2 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;  
3 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients  
4 was atherosclerosis, while the primary risk faced by very-high TG patients was acute  
5 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for  
6 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for  
7 very-high TG patients was TG reduction. This distinction between patients with borderline-  
8 high/high TG levels and patients with very high TG levels is also observed on the regulatory  
9 level. The FDA recognized the different clinical status of the very-high TG population by  
10 approving some drugs specifically for the very-high TG group without granting treatment  
11 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).<sup>2407</sup>

12 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the  
13 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the  
14 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known  
15 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the  
16 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG  
17 level of the patient receiving treatment.

18 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but  
19 *increase* LDL-C in very-high TG patients.<sup>2408</sup> The fibrate, Tricor (fenofibrate), for example,  
20 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)<sup>2409</sup>

21  
22 <sup>2407</sup> See Bays Jan. 8, 2012 Decl., ¶ 22.

23 <sup>2408</sup> See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain  
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

24 <sup>2409</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).<sup>2410</sup> In  
 2 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-  
 3 significant increase in LDL-C was observed.<sup>2411</sup> In patients with very-high TGs (mean baseline  
 4 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).<sup>2412</sup> Similar  
 5 results were seen with the administration of Lopid (gemfibrozil).<sup>2413</sup> The differing effects of  
 6 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values  
 7 demonstrates how a person of ordinary skill at the time of the invention would have understood  
 8 that one could not simply assume that an observed effect of a TG-lowering agent on lipid  
 9 parameters in patients with normal, borderline-high or high TG levels would be the same in  
 10 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or  
 11 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with  
 12 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-  
 13 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean  
 14 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level  
 15 of 726 mg/dL) experience significantly increased LDL-C levels.

<b>Fibrate</b>	<b>Mean Baseline TG Value</b>	<b>TG</b>	<b>LDL-C</b>	<b>HDL-C</b>	<b>Total-C</b>
Tricor (fenofibrate) <sup>2414</sup>	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*

20 <sup>2410</sup> *Id.*

21 <sup>2411</sup> *Id.* See also, Trilipix Label at 27.

22 <sup>2412</sup> *Id.* See also, Trilipix Label at 27.

23 <sup>2413</sup> See *Otvos* at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); *Manttari* at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

24 <sup>2414</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

\* = p < 0.05 vs. Placebo

Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing lipid effects depending on the patient’s baseline TG level. When administered to patients with borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-C.<sup>2415</sup> It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.<sup>2416</sup> However, when administered to patients with very-high baseline TG levels, TGs were reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.<sup>2417</sup> Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>2418</sup>

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG

<sup>2415</sup> Chan 2002 I at 2379-81.

<sup>2416</sup> *Id.*; See also, Westphal at 918.

<sup>2417</sup> See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

<sup>2418</sup> See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”)

1 levels ( $\geq 500$  mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They  
2 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when  
3 the normal, borderline-high or high TG patient populations were administered omega-3 fatty  
4 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was  
5 expected as a natural consequence of lowering TGs. A person of ordinary skill would have  
6 considered the rise in LDL-C to be a direct consequence of TG lowering through increased  
7 VLDL particle conversion.<sup>2419</sup> Because normal to high TG patients did not have the large  
8 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not  
9 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree  
10 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,  
11 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the  
12 highest baseline TG levels<sup>2420</sup> and did not increase for patients with lower TG levels. Therefore,  
13 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,  
14 borderline-high or high TG patients was *expected*.

15 Defendants contend that “a composition and its properties are inseparable, and therefore  
16 do not impart any additional patentability,” and that “all of the limitations regarding the  
17 pharmacologic properties of the ethyl EPA compound identified in the claims of the ‘677 patent  
18 are inherent to the compound when administered to a human subject.”<sup>2421</sup> Inherency may not

19 \_\_\_\_\_  
20 <sup>2419</sup> Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class  
21 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels  
22 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during  
treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some  
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the  
decrease in VLDL.”).

23 <sup>2420</sup> Bays 2008 I at 400-402.

24 <sup>2421</sup> Defendants’ Joint Invalidity Contentions at 311.



1 supply a missing claim limitation in an obviousness analysis unless the inherency would have  
2 been obvious to one of ordinary skill in the art.<sup>2422</sup> Obviousness is based on what is *known* in the  
3 art at the time of the invention.<sup>2423</sup> It was not known or reasonably expected at the time of the  
4 claimed invention that purified EPA, when administered to patients with very-high TG levels  
5 ( $\geq 500$  mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's  
6 effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of  
7 elements explicitly disclosed by the prior art.<sup>2424</sup> Therefore, inherency does not supply the  
8 missing claim elements in the prior art cited by Defendants.

9 Defendants argue that the claims of the '677 patent which contain "a limiting clause, such  
10 as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively  
11 recited and therefore are not elements.<sup>2425</sup> This is incorrect. "There is nothing inherently wrong  
12 with defining some part of an invention in functional terms."<sup>2426</sup> When a clause "states a  
13 condition that is material to patentability, it cannot be ignored in order to change the substance of  
14 the invention."<sup>2427</sup> The claim term "to effect" acts as a positive limitation if the term represents

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17 <sup>2422</sup> See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) ("A party must . . .  
18 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an  
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of  
19 elements explicitly disclosed by the prior art."); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) ("The mere  
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].")  
(internal quotation omitted).

20 <sup>2423</sup> *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known.  
Obviousness cannot be predicated on what is unknown.").

21 <sup>2424</sup> See discussions below for *Grimsgaard*, *Park*, *Nozaki Kurabayashi* and *Hayashi*.

22 <sup>2425</sup> Defendants' Joint Invalidity Contentions at 312.

23 <sup>2426</sup> See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 <sup>2427</sup> *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

1 “unexpected and improved effects of administration of the claimed compound.”<sup>2428</sup> In addition,  
2 the elements represent unexpected and improved effects of administration of purified EPA,  
3 because a person of ordinary skill would not have expected no substantial increase in LDL-C or  
4 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the  
5 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded  
6 patentable weight.

7 b) Identification of Claim Elements Absent from Each Item of Prior  
8 Art

9 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.  
10 Where a limitation is absent from any Independent Claim, that limitation is absent from all  
11 asserted claims, and that analysis is incorporated by reference into each dependent claim. For  
12 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted  
13 claims is not a concession that such limitation is present in the reference. By discussing  
14 Defendants’ analysis of the “limitations” in the claims, Plaintiffs do not concede that Defendants  
15 have appropriately divided the claim language for any purpose.

16 (1) WO ‘118

17 WO ‘118 discloses a composition containing EPA-E for preventing the occurrence of  
18 cardiovascular events in multiple risk patients.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
20 ‘118 disclose or suggest elements of the ‘677 Claims. The cited portions of WO ‘118 do not  
21 disclose or suggest these elements at least because they do not disclose or suggest administration  
22 of EPA with the recited purity to a subject with the recited very high TG levels. The cited

23 \_\_\_\_\_  
24 <sup>2428</sup> AstraZeneca AB v. Dr. Reddy’s Labs., Ltd., No. CIV.A.05-5553 JAP, 2010 WL 1981790, at \*11–12 (D.N.J.  
May 18, 2010).

1 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition  
2 with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not  
3 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
4 LDL-C based on a comparison to placebo control.

5 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), WO '118  
6 does not disclose or suggest a subject with the recited very high TG level. WO '118 also does  
7 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids  
8 compositions or dosage. WO '118 further does not disclose or suggest a method to effect the  
9 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
10 control.

11 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
12 having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to  
13 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
14 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
15 Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
16 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
17 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
18 subject with the claimed TG levels based on a comparison to placebo control.

19 (2) WO '900

20 WO '900 describes methods for obtaining EPA-rich compositions.

21 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
22 '900 disclose or suggest elements of the '677 Claims. The cited portions of WO '900 do not  
23 disclose or suggest these elements at least because they do not disclose or suggest administration  
24 of EPA with the recited purity to a subject with the recited very high TG levels. The cited

1 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition  
2 with the recited fatty acid dosage or administration period. The cited portions of WO '900  
3 further do not disclose or suggest a method to effect the recited TG reduction without  
4 substantially increasing LDL-C based on a comparison to placebo control.

5 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), WO '900  
6 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does  
7 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
8 dosage or administration period. WO '900 further does not disclose or suggest a method to  
9 effect the recited TG reduction without substantially increasing LDL-C based on a comparison to  
10 placebo control.

11 Further, with respect to Claim 2, this reference does not disclose or suggest  
12 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
13 disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claim 5,  
14 this reference fails to disclose or suggest the subject having the recited baseline lipid levels.  
15 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in  
16 TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a  
17 comparison to placebo control. With respect to Claim 8, this reference fails to disclose or  
18 suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based  
19 on a comparison to placebo control. With respect to Claim 9, this reference fails to disclose or  
20 suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a  
21 comparison to placebo control.

22 (3) Contacos

23 Contacos describes a study designed to determine the safety and efficacy of a statin  
24 (pravastatin) combined with fish oil either alone or in combination, for the management of

1 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in  
2 the claims.

3 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
4 Contacos disclose or suggest elements of the '677 Claims. The cited portions of Contacos do not  
5 disclose or suggest these elements at least because they do not disclose or suggest administration  
6 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
7 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition  
8 with the recited fatty acid compositions, dosage, or administration period. The cited portions of  
9 Contacos does not disclose or suggest a method of administering the claimed pharmaceutical  
10 composition to effect the recited TG reduction without substantially increasing LDL-C based on  
11 a comparison to a placebo control.

12 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Contacos  
13 does not disclose or suggest a subject with the recited very high TG level. Contacos also does  
14 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
15 compositions, dosage, or administration period. Contacos further does not disclose or suggest a  
16 method of administering the claimed pharmaceutical composition to effect the recited TG  
17 reduction without substantially increasing LDL-C based on a comparison to placebo control.

18 Further, with respect to Claim 2, this reference does not disclose or suggest  
19 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
20 disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims  
21 6 and 7, this reference fails to disclose or suggest the administration of the claimed  
22 pharmaceutical composition to effect the recited reduction in TG without substantially increasing  
23 LDL-C based on a comparison to placebo control. With respect to Claim 8, this reference fails  
24

1 to disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
2 recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to  
3 Claim 9, this reference fails to disclose or suggest the administration of the claimed  
4 pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to  
5 placebo control.

6 (4) Grimsgaard

7 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design  
8 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,  
9 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG  
10 levels.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
12 Grimsgaard disclose or suggest elements of '677 Claims. The cited portions of Grimsgaard do  
13 not disclose or suggest these elements at least because they do not disclose or suggest  
14 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
15 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical  
16 composition with the recited fatty acid compositions or administration period. The cited portions  
17 of Grimsgaard does not disclose or suggest a method of administering the claimed  
18 pharmaceutical composition to effect the recited TG reduction without substantially increasing  
19 LDL-C based on a comparison to a placebo control.

20 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Grimsgaard  
21 does not disclose or suggest a subject with the recited very high TG levels. Grimsgaard also  
22 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
23 compositions or administration period. Grimsgaard further does not disclose or suggest a  
24

1 method of administering the claimed pharmaceutical composition to effect the recited TG  
2 reduction without substantially increasing LDL-C based on a comparison to a placebo control.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
4 having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to  
5 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
6 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
7 Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
8 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
9 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
10 subject with the claimed TG levels based on a comparison to placebo control.

11 (5) Hayashi

12 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for  
13 8 weeks. The purity of the composition is not reported. The study was not placebo controlled  
14 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride  
15 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220  
16 mg/dl.

17 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the  
18 '677 patent claims. For example, the cited portions of Hayashi do not disclose or suggest  
19 administration of EPA with the recited purity to a subject with the recited very high TG levels  
20 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject  
21 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or  
22 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or  
23 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the  
24

1 recited TG reduction without substantially increasing LDL-C in a subject with the recited very  
2 high TG levels.

3 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Hayashi  
4 does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not  
5 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
6 compositions or dosage. Hayashi further does not disclose or suggest a method to effect the  
7 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
8 control.

9 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
10 having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to  
11 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
12 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
13 Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
14 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
15 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
16 subject with the claimed TG levels based on a comparison to placebo control.

17 (6) Katayama

18 Katayama was directed to an investigation of the safety and efficacy of Epadel during  
19 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,  
20 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and  
21 was not placebo controlled.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
23 Katayama disclose or suggest elements of the '677 Claims. The cited portions of Katayama do  
24 not disclose or suggest these elements at least because they do not disclose or suggest



1 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
2 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical  
3 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama  
4 further do not disclose or suggest a method to effect the recited TG reduction without  
5 substantially increasing LDL-C based on a comparison to placebo control.

6 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Katayama  
7 does not disclose or suggest a subject with the recited very high TG level. Katayama also does  
8 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or dosage. Katayama further does not disclose or suggest a method to effect the  
10 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
11 control.

12 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
13 having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to  
14 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
15 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
16 Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
17 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
18 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
19 subject with the claimed TG levels based on a comparison to placebo control.

20 (7) Leigh-Firbank

21 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle  
22 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank  
23 does not administer EPA of the purity recited in the claims.  
24

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
2 Leigh-Firbank disclose or suggest elements of the '677 Claims. The cited portions of Leigh-  
3 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest  
4 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
5 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed  
6 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration  
7 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of  
8 administering the claimed pharmaceutical composition to effect to effect the recited TG  
9 reduction without substantially increasing LDL-C based on a comparison to placebo control.

10 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Leigh-  
11 Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-  
12 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the  
13 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not  
14 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
15 to effect the recited TG reduction without substantially increasing LDL-C based on a comparison  
16 to placebo control.

17 Further, with respect to Claim 2, this reference does not disclose or suggest  
18 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
19 disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims  
20 6 and 7, this reference fails to disclose or suggest the administration of the claimed  
21 pharmaceutical composition to effect the recited reduction in TG without substantially increasing  
22 LDL-C based on a comparison to placebo control. With respect to Claim 8, this reference fails  
23 to disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
24

1 recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to  
2 Claim 9, this reference fails to disclose or suggest the administration of the claimed  
3 pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to  
4 placebo control.

5 (8) Lovaza PDR

6 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
8 Lovaza PDR disclose or suggest elements of the '677 Claims. The cited portions of the Lovaza  
9 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
10 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
11 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed  
12 pharmaceutical composition with the recited fatty acid compositions or administration period.  
13 The cited portions of the Lovaza PDR further do not disclose or suggest a method to effect the  
14 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
15 control.

16 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), the Lovaza  
17 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
18 acid compositions or administration period. The Lovaza PDR further does not disclose or  
19 suggest a method to effect the recited TG reduction without substantially increasing LDL-C  
20 based on a comparison to placebo control.

21 Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the  
22 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
23 placebo control. With respect to Claim 8, this reference fails to disclose or suggest the recited  
24 reduction in Apolipoprotein B based on a comparison to placebo control.

1 (9) Maki

2 Maki administered 1.52g/day DHA supplements to patients with below-average levels of  
3 HDL-C. Maki does not administer EPA of the purity recited in the claims.

4 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki  
5 disclose or suggest elements of the '677 Claims. The cited portions of Maki do not disclose or  
6 suggest these elements at least because they do not disclose or suggest administration of EPA  
7 with the recited purity to a subject with the recited very high TG levels. The cited portions of  
8 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited  
9 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do  
10 not disclose or suggest a method of administering the claimed pharmaceutical composition to  
11 effect the recited TG reduction without substantially increasing LDL-C based on a comparison to  
12 placebo control.

13 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Maki does  
14 not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose  
15 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,  
16 dosage, or administration period. Maki further does not disclose or suggest a method of  
17 administering the claimed pharmaceutical composition to effect the recited TG reduction without  
18 substantially increasing LDL-C based on a comparison to placebo control.

19 With respect to Claim 2, this reference does not disclose or suggest administration of the  
20 claimed pharmaceutical composition to the subject 1 to 4 times per day. With respect to Claim  
21 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level.  
22 With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of  
23 the claimed pharmaceutical composition to effect the recited reduction in TG without  
24 substantially increasing LDL-C based on a comparison to placebo control. With respect to

1 Claim 8, this reference fails to disclose or suggest the administration of the claimed  
2 pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a  
3 comparison to placebo control. With respect to Claim 9, this reference fails to disclose or  
4 suggest the administration of the claimed pharmaceutical composition to effect the recited  
5 reduction in VLDL-C based on a comparison to placebo control.

6 (10) Matsuzawa

7 Matsuzawa administered Epadel ® to patients with hyperlipaemia in order to study its  
8 long-term use in the treatment of the disease and was not placebo controlled.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
10 Matsuzawa disclose or suggest elements of the '677 Claims. The cited portions of Matsuzawa  
11 do not disclose or suggest these elements at least because they do not disclose or suggest  
12 administration of EPA with the recited purity to a subject with the recited very high TG levels  
13 who does not receive concurrent lipid altering therapy. The cited portions of Matsuzawa further  
14 do not disclose or suggest these elements because they do not disclose or suggest the claimed  
15 pharmaceutical composition with the recited fatty acid compositions or dosage. The cited  
16 portions of Matsuzawa further do not disclose or suggest a method of administering the claimed  
17 pharmaceutical composition to effect the recited TG reduction without substantially increasing  
18 LDL-C based on a comparison to placebo control.

19 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Matsuzawa  
20 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
21 compositions, dosage, or administration period. Matsuzawa further does not disclose or suggest  
22 a method of administering the claimed pharmaceutical composition to effect the recited TG  
23 reduction without substantially increasing LDL-C based on a comparison to placebo control.  
24

1 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
2 having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to  
3 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
4 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
5 placebo control. With respect to Claim 8, this reference fails to disclose or suggest the  
6 administration of the claimed pharmaceutical composition to effect the recited reduction in  
7 Apolipoprotein B based on a comparison to placebo control. With respect to Claim 9, this  
8 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
9 composition to effect the recited reduction in VLDL-C based on a comparison to placebo  
10 control.

11 (11) Mori 2000 [EPA  $\approx$  96%; 6 weeks; NS increase in LDL-C]

12 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum  
13 lipids and lipoproteins, glucose and insulin in humans.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
15 2000 disclose or suggest elements of the '677 Claims. The cited portions of Mori 2000 do not  
16 disclose or suggest these elements at least because they do not disclose or suggest administration  
17 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
18 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition  
19 with the recited fatty acid compositions or administration period. The cited portions of Mori  
20 2000 further do not disclose or suggest a method of administering the claimed pharmaceutical  
21 composition to effect the recited TG reduction without substantially increasing LDL-C in the  
22 subject with the claimed TG levels based on a comparison to placebo control.

23 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Mori 2000  
24 does not disclose or suggest a subject with the recited very high TG levels. Mori 2000 further

1 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions or administration period. Mori 2000 further does not disclose or suggest a method  
3 of administering the claimed pharmaceutical composition to effect the recited TG reduction  
4 without substantially increasing LDL-C in the subject with the claimed TG levels based on a  
5 comparison to placebo control.

6 Further, with respect to Claim 2, this reference does not disclose or suggest  
7 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
8 disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims  
9 6 and 7, this reference fails to disclose or suggest the recited reduction in TG without  
10 substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison  
11 to placebo control. With respect to Claim 8, this reference fails to disclose or suggest the recited  
12 reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison  
13 to placebo control. With respect to Claim 9, this reference fails to disclose or suggest the recited  
14 reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to  
15 placebo control.

16 (12) Mori 2006

17 Mori 2006 is a review which reports data from clinical trials which compared the  
18 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
20 2006 disclose or suggest elements of the '677 Claims. The cited portions of Mori 2006 do not  
21 disclose or suggest these elements at least because they do not disclose or suggest administration  
22 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
23 portions of Mori 2006 further do not disclose or suggest administration of the claimed  
24 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration

1 period to a subject with the claimed TG level. The cited portions of Mori 2006 further do not  
2 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
3 LDL-C in a subject with the claimed TG levels based on a comparison to placebo control.

4 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Mori 2006  
5 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does  
6 not disclose or suggest administration of the claimed pharmaceutical composition with the  
7 recited fatty acid compositions, dosage, or administration period to a subject with the claimed  
8 TG level. Mori 2006 further does not disclose or suggest a method to effect the recited TG  
9 reduction without substantially increasing LDL-C in a subject with the claimed TG levels based  
10 on a comparison to placebo control.

11 Further, with respect to Claim 2, this reference does not disclose or suggest  
12 administration to the subject 1 to 4 times per day. Further, with respect to Claim 4, this reference  
13 fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to  
14 Claim 5, this reference fails to disclose or suggest the subject having the recited baseline lipid  
15 levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited  
16 reduction in TG without substantially increasing LDL-C in the subject with the claimed TG  
17 levels based on a comparison to placebo control. With respect to Claim 8, this reference fails to  
18 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
19 levels based on a comparison to placebo control. With respect to Claim 9, this reference fails to  
20 disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels  
21 based on a comparison to placebo control.

22 (13) Nozaki

23 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The  
24 purity of the composition is reported as 90%. The study was not placebo controlled and was



1 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165  
2 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG  
3 patient population.

4 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the  
5 '677 patent claims. For example, the cited portions of Nozaki do not disclose or suggest  
6 administration of EPA with the recited purity to a subject with the recited very high TG levels  
7 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do  
8 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a  
10 method to effect the recited TG reduction without substantially increasing LDL-C in a subject  
11 with the recited very high TG levels.

12 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the  
13 '677 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least  
14 because they do not disclose or suggest administration of EPA with the recited purity to a subject  
15 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The  
16 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical  
17 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki  
18 further do not disclose or suggest a method to effect the recited TG reduction without  
19 substantially increasing LDL-C.

20 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Nozaki  
21 does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not  
22 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
23 compositions or dosage. Nozaki further does not disclose or suggest a method to effect the  
24

1 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
2 control.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
4 having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to  
5 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
6 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
7 Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
8 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
9 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
10 subject with the claimed TG levels based on a comparison to placebo control.

11 (14) Omacor PDR

12 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
14 Omacor PDR disclose or suggest elements of the '677 Claims. The cited portions of the Omacor  
15 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
16 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
17 The cited portions of the Omacor PDR further do not disclose or suggest the claimed  
18 pharmaceutical composition with the recited fatty acid compositions or administration period.  
19 The cited portions of the Omacor PDR further do not disclose or suggest a method to effect the  
20 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
21 control.

22 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), the Omacor  
23 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
24 acid compositions or administration period. The Omacor PDR further does not disclose or

1 suggest a method to effect the recited TG reduction without substantially increasing LDL-C  
2 based on a comparison to placebo control.

3 Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the  
4 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
5 placebo control. With respect to Claim 8, this reference fails to disclose or suggest the recited  
6 reduction in Apolipoprotein B based on a comparison to placebo control.

7 (15) Satoh

8 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
9 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
10 systemic inflammation.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
12 Satoh disclose or suggest elements of the '677 Claims. The cited portions of Satoh do not  
13 disclose or suggest these elements at least because they do not disclose or suggest administration  
14 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
15 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with  
16 the recited fatty acid compositions or dosage. The cited portions of Satoh further do not disclose  
17 or suggest a method of administering the claimed pharmaceutical composition to effect the  
18 recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG  
19 levels based on a comparison to placebo control.

20 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Satoh does  
21 not disclose or suggest a subject with the recited very high TG levels. Satoh further does not  
22 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
23 compositions or dosage. Satoh further does not disclose or suggest a method of administering  
24 the claimed pharmaceutical composition to effect the recited TG reduction without substantially

1 increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo  
2 control.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
4 having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to  
5 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
6 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
7 Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
8 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
9 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
10 subject with the claimed TG levels based on a comparison to placebo control.

11 (16) Shinozaki

12 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and  
13 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
15 Shinozaki disclose or suggest elements of the '677 Claims. The cited portions of Shinozaki do  
16 not disclose or suggest these elements at least because they do not disclose or suggest  
17 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
18 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical  
19 composition with the recited fatty acid dosage. The cited portions of Shinozaki further do not  
20 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
21 the recited TG reduction without substantially increasing LDL-C in the subject with the claimed  
22 TG levels based on a comparison to placebo control.

23 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Shinozaki  
24 does not disclose or suggest a subject with the recited very high TG levels. Shinozaki further

1 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 dosage. Shinozaki further does not disclose or suggest a method of administering the claimed  
3 pharmaceutical composition to effect the recited TG reduction without substantially increasing  
4 LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

5 Further, with respect to Claim 2, this reference does not disclose or suggest  
6 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
7 disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claim 5,  
8 this reference fails to disclose or suggest the subject having the recited baseline lipid levels.  
9 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in  
10 TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a  
11 comparison to placebo control. With respect to Claim 8, this reference fails to disclose or  
12 suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based  
13 on a comparison to placebo control. With respect to Claim 9, this reference fails to disclose or  
14 suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a  
15 comparison to placebo control.

16 (17) Takaku

17 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-  
18 term use and was not placebo controlled.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
20 Takaku disclose or suggest elements of the '677 Claims. The cited portions of Takaku do not  
21 disclose or suggest these elements at least because they do not disclose or suggest administration  
22 of EPA with the recited purity to a subject with the recited very high TG levels who does not  
23 receive concurrent lipid altering therapy. The cited portions of Takaku further do not disclose or  
24 suggest these elements because they do not disclose or suggest the claimed pharmaceutical

1 composition with the recited fatty acid compositions or dosage. The cited portions of Takaku  
2 further do not disclose or suggest a method of administering the claimed pharmaceutical  
3 composition to effect the recited TG reduction without substantially increasing LDL-C based on  
4 a comparison to placebo control.

5 With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Takaku  
6 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
7 compositions, dosage, or administration period. Takaku further does not disclose or suggest a  
8 method of administering the claimed pharmaceutical composition to effect the recited TG  
9 reduction without substantially increasing LDL-C based on a comparison to placebo control.

10 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
11 having the recited baseline LDL-C level. With respect to Claim 5, this reference fails to disclose  
12 or suggest the subject having the recited baseline lipid levels. With respect to Claims 6 and 7,  
13 this reference fails to disclose or suggest the recited reduction in TG without substantially  
14 increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo  
15 control. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction  
16 in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo  
17 control. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction  
18 in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

19 c) The Prior Art Does Not Render the Claims Obvious

20 Defendants have not identified by clear and convincing evidence that the asserted claims  
21 of the '677 Patent would have been *prima facie* obvious in light of the references cited, either  
22 alone or in combination. As described above, none of the references discloses all of the elements  
23 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without  
24 explanation, and argue they somehow must be combined to render obvious the asserted claims.

1 Where Defendants have failed to make disclosures with the specificity required by Local Patent  
2 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the  
3 claim elements at issue.

4 Defendants' contentions fail to disclose each and every element of the claims of the '677  
5 patent. Specifically, Defendants do not contend that the relied upon references disclose the  
6 following elements of Claim 1 (and therefore Claims 2-9): *administering the claimed*  
7 *pharmaceutical composition to the recited subject to effect a reduction in triglycerides without*  
8 *substantially increasing LDL-C compared to placebo control.* Therefore, Defendants' prior art  
9 combinations cannot render the claims *prima facie* obvious.

10 Facts supporting the non-obviousness of the claims of the '677 patent are discussed in  
11 detail below. The objective indicia discussed in Section V.O further demonstrate that the '677  
12 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims  
13 would have been obvious.

- 14 (1) Defendants Do Not Demonstrate that the Independent  
15 Claim of the '677 Patent Would Have Been Obvious
  - 16 (a) Defendants Do Not Demonstrate that a Person of  
17 Ordinary Skill in the Art Would Have Had Any  
Reason to Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with Pure EPA
  - 18 (i) The '677 Patent is not Obvious Over the  
19 Omacor PDR/Lovaza PDR, in Combination  
with Katayama and/or Matsuzawa, Further  
20 in View of Nozaki and/or Hayashi and  
Further in View of Leigh-Firbank and/or  
21 Mori 2000

22 With respect to the '677 Patent, Defendants present a combination of seven references:  
23 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering  
24 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or

1 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000.”<sup>2429</sup> Defendants also present  
2 charts purporting to assert that an additional 61 references may be combined in order to render  
3 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary  
4 skill would combine 61 separate references, they additionally do not identify any motivation for  
5 combining these references.<sup>2430, 2431</sup> Although Defendants need not point to an explicit statement  
6 in the prior art motivating the combination of these references, any assertion of an “apparent  
7 reason” to combine must find a basis in the factual record.<sup>2432</sup> Defendants’ unsupported cobbling  
8  
9

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10 <sup>2429</sup> Defendants’ Joint Invalidity Contentions at 305.

11 <sup>2430</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as  
12 described in the references cited above in section V.B.2) in view of, at least, the references cited in V.B.3 and 4,  
13 including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matakai,  
14 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,  
15 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006,  
16 Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent  
17 Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity  
18 Contentions at 304-05.

19 <sup>2431</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
20 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
21 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person  
22 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
23 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
24 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 303-04.

<sup>2432</sup> *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi  
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).



1 of selective disclosures represents hindsight reconstruction.<sup>2433</sup> Defendants’ contentions are no  
2 more than an assertion that certain claim elements were known in the prior art. Throughout their  
3 contentions, Defendants’ selectively cite to data points in a reference without considering other  
4 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
5 that it teaches.<sup>2434</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
6 obviousness.

7 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
8 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed  
9 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a  
10 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the  
11 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a  
12 significant increase in LDL-C levels in the very high TG patient population, for whom the  
13 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,  
14 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce  
15 TG levels in adult patients with very-high ( $\geq 500$  mg/dL) TG levels.

16 The proposed combinations do not render the independent claim of the ’677 Patent  
17 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
18 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza  
19 package insert specifically) during prosecution.<sup>2435</sup>

20  
21 <sup>2433</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
22 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 <sup>2434</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>2435</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.

1 The analysis of the independent claim of the '677 Patent is incorporated into all asserted  
2 claims that depend from this Claim.

3 (a) A Person of Ordinary Skill Would  
4 Not Have Been Motivated to  
5 Replace the Mixed Fish Oil Active  
6 **Ingredient in Lovaza with Pure  
7 EPA**

6 For an invention to be obvious, there must have been an “apparent reason” to make it.  
7 The subject matter of the '677 patent claims would not have been obvious in light of these  
8 references because a person of ordinary skill would not have been motivated to purify EPA or  
9 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
10 levels without an increase in LDL-C levels.

11 (i) Katayama and/or Matsuzawa  
12 Do Not Disclose Purported  
13 Known Clinical Benefits of  
14 Administering Pure EPA

13 Both Katayama and Matsuzawa are long term studies directed to an investigation of the  
14 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies  
15 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may  
16 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the  
17 art would not and could not attribute any observed effect (and the magnitude of that effect) to  
18 that of the drug. Any observed effect could be placebo dependent.<sup>2436</sup> As discussed above in  
19 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with  
20

21  
22 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

23 <sup>2436</sup>See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a  
24 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a  
placebo-controlled study and why results compared only to baseline may be misleading.)

1 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG  
2 patients because patients with higher TG levels had different lipid responses compared to  
3 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally  
4 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical  
5 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary  
6 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were  
7 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art  
8 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-  
9 high or high TG patients, was expected. At the priority date of the ‘677 patent, a person of  
10 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients  
11 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been  
12 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG  
13 lowering through increased VLDL particle conversion.

14 Defendants argue that these studies disclose known “clinical benefits” of administering  
15 pure EPA, lowering triglycerides without raising LDL-C.<sup>2437</sup> This is an incorrect characterization  
16 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of  
17 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.  
18 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.  
19 Defendants’ selective citation of LDL-C data from these references represents the improper use  
20 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and  
21 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw  
22 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C

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23  
24 <sup>2437</sup> Defendants’ Joint Invalidity Contentions at 305 and 306.

1 levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the  
2 lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.<sup>2438</sup> The  
3 references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor  
4 would a person of ordinary skill view these references as teaching such a benefit for very-high  
5 TG patients.

6 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid  
7 effects. These studies fail to provide a head to head comparison of EPA versus DHA.  
8 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to  
9 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

10 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The  
11 purity of Epadel has varied over time and across different formulations of the product, therefore  
12 it is difficult to determine the purity of the version of Epadel used unless it is specified by the  
13 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the  
14 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and  
15 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference  
16 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

17 Nishikawa,<sup>2439</sup> published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.  
18 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite  
19 purity.<sup>2440</sup>

22 <sup>2438</sup> Defendants' Joint Invalidity Contentions at 305.

23 <sup>2439</sup> Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS  
Analysis of PGI<sub>2</sub> and PGI<sub>3</sub> Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 <sup>2440</sup> See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

1 Further, Katayama and Matsuzawa were small studies conducted in only Japanese  
2 patients. These studies would not have been extrapolated to Western populations because the  
3 Japanese diet contains much more fish and has a number of other different attributes. The  
4 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In  
5 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where  
6 the patient population is exclusively Japanese cannot be generalized to other populations.<sup>2441</sup>  
7 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical  
8 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-  
9 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand  
10 that the Japanese respond differently to lipid lowering agents than Westerners.

11 Defendants rely on Katayama to demonstrate the "known clinical benefits of  
12 administering pure EPA - lowering triglycerides without raising LDL-C."<sup>2442</sup> However,  
13 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term  
14 treatment in patients with hyperlipidemia.<sup>2443</sup> Katayama does not disclose *any* LDL-C related  
15 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that  
16 reference to provide any such disclosure. The only results disclosed by Katayama were a  
17 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was  
18 administered to patients with borderline-high to high TG levels, and its safety for long term use  
19 in this patient population.<sup>2444</sup> In addition to Katayama's lack of disclosure regarding LDL-C,  
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21 <sup>2441</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

22 <sup>2442</sup> Defendants' Joint Invalidity Contentions at 305 and 306.

23 <sup>2443</sup> Katayama at 2.

24 <sup>2444</sup> *Id.* at 16.

1 Defendants identify no other basis upon which a person of ordinary skill would have sought to  
2 combine the composition disclosed in Katayama with the Lovaza PDR.

3 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of  
4 administering pure EPA - lowering triglycerides without raising LDL-C.”<sup>2445</sup> However,  
5 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall  
6 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of  
7 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13  
8 were evaluated for improvement in serum triglycerides levels.<sup>2446</sup> It is unclear which of the 26  
9 patients were included in each separate evaluation; therefore one cannot determine the baseline  
10 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack  
11 of a placebo control makes it less likely that the results of this study can be generalized as an  
12 effect on any population as a whole and provides no insight with respect to the very-high TG  
13 patient population.

14 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,  
15 and one participant with TG levels > 1,000 mg/dL.<sup>2447</sup> However, when analyzing the lipid  
16 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL  
17 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess  
18 triglyceride levels.”<sup>2448</sup> Fig. 4, which depicts the changes in serum triglycerides, shows that the  
19 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500  
20 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than

21  
22 <sup>2445</sup> Defendants’ Joint Invalidation Contentions at 305 and 306.

23 <sup>2446</sup> Matsuzawa at 7 and 19.

24 <sup>2447</sup> *Id.* at 23.

<sup>2448</sup> *Id.* at 10.

1 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of  
2 undisclosed purity). The identification of three patients with TG levels between 400 and less  
3 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of  
4 ordinary skill would not understand that the reference makes any such disclosure. As discussed  
5 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG  
6 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no  
7 evidence to the contrary.

8 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a  
9 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.<sup>2449</sup> The disclosure  
10 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were  
11 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-  
12 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at  
13 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with  
14 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of  
15 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary  
16 skill in the art, however, would have expected the same treatment in patients with very high TG  
17 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that  
18 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered  
19 triglyceride levels.<sup>2450</sup> At best, Matsuzawa demonstrates the uncertainty and confusion related to  
20 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify

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22 <sup>2449</sup> *Id.* at 11.

23 <sup>2450</sup> *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA  
24 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific  
compositions used, or identify the patient populations were observed.

1 any other basis upon which a person of ordinary skill would have sought to combine the  
2 composition disclosed in Matsuzawa with the Lovaza PDR.

3 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that  
4 compositions comprising EPA as recited in the asserted claims lowers triglycerides without  
5 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA  
6 increases LDL-C.<sup>2451</sup> Defendants identify no other basis upon which a person of ordinary skill  
7 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank  
8 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the  
9 asserted claims of the '677 patent.

10 (ii) Nozaki and/or Hayashi  
11 Would Not Have Rendered  
12 the Asserted Claims Obvious

12 Defendants contend that the asserted claims of the '677 patent would have been obvious  
13 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
14 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
15 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
16 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
17 very high TG patient population.

18 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
19 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
20 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
21 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
22 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person

23  
24 <sup>2451</sup> See, e.g., Rambjor.



1 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
2 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
3 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
4 patient population were abnormally high and would not have relied upon these results. Further,  
5 the person of skill in the art would not have looked to this patient population to predict the Apo-  
6 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
7 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
8 levels.<sup>2452</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
9 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
10 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
11 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
12 to the very high TG patient population.

13 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
14 the EPA and the DHA content in the composition that was administered is unknown. A person  
15 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
16 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
17 C were not statistically significant.<sup>2453</sup> Further, the person of skill in the art would not have  
18 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
19 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
20 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
21 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
22

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23 <sup>2452</sup> Nozaki at 256.

24 <sup>2453</sup> Hayashi at 26, Table I.

1 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
2 administered to the very high TG patient population.

3 Further, Hayashi was a small study conducted in only Japanese patients and was not  
4 placebo controlled. This study would not have been extrapolated to Western populations  
5 because the Japanese diet contains much more fish and has a number of other different attributes.  
6 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
7 populations. In fact, Defendants' own reference states that the results from studies where the  
8 patient population is exclusively Japanese cannot be generalized to other populations.<sup>2454</sup> The  
9 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
10 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
11 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
12 the Japanese respond differently to lipid lowering agents than Westerners.

13 Further, Defendants have failed to offer a purported combination of references as part of  
14 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
15 motivation to combine Nozaki and Hayashi with the other references of their purported  
16 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
17 references.

18 (iii) Leigh-Firbank and/or Mori  
19 2000 Do Not Disclose  
20 Purported Knowledge that  
21  
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23 <sup>2454</sup> Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to  
24 other populations.”).

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2  
3 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
4 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
5 C levels.”<sup>2455</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
6 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
7 rely upon to support this statement does not categorize the increase in LDL-C as a “negative  
8 effect” in light of the overall impact of the disclosed composition on all lipid parameters.  
9 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As  
10 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
11 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—  
12 as in very-high TG patients because patients with higher TG levels had different lipid responses  
13 compared to patients with lower TG levels. Patients with very-high TG levels were considered  
14 fundamentally different from patients with borderline-high or high triglycerides from a lipid  
15 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person  
16 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)  
17 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but  
18 would substantially increase LDL-C in patients with very high TG levels.

19 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was  
20 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,  
21 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride  
22 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either

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24 <sup>2455</sup> Defendants’ Joint Invalidity Contentions at 308.

1 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A  
2 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any  
3 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the  
4 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)  
5 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated  
6 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA  
7 and DHA.<sup>2456</sup> A person of ordinary skill would understand that studies directed to EPA and  
8 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on  
9 lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-  
10 Firbank, because purified EPA and DHA were not administered separately.

11 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent  
12 effects of EPA and DHA individually, even though it administered a combination of EPA and  
13 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions  
14 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet  
15 phospholipid EPA were *independently* associated with the decrease in fasting TGs,<sup>2457</sup> and DHA  
16 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state  
17 of the art and numerous publications cited by Defendants.<sup>2458</sup> It is widely accepted that DHA  
18 also has a hypotriglyceridemic effect.

19 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients  
20 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-  
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22 <sup>2456</sup> Mori 2006 at 96.

23 <sup>2457</sup> Leigh-Firbank at 440.

24 <sup>2458</sup> See, e.g. Grimsgaard at 654.

1 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching  
2 away from the claimed invention. “A reference may be said to teach away when a person of  
3 ordinary skill, upon [examining] the reference, would be discouraged from following the path set  
4 out in the reference, or would be led in a direction divergent from the path that was taken by the  
5 applicant.”<sup>2459</sup> Although teaching away is fact-dependent, “in general, a reference will teach  
6 away if it suggests that the line of development flowing from the reference’s disclosures is  
7 unlikely to be productive of the result sought by the applicant.”<sup>2460</sup>

8 Mori 2000 concludes that the changes effected by DHA supplementation “may represent  
9 a more favorable lipid profile than after EPA supplementation.”<sup>2461</sup> For example, it states that  
10 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL  
11 cholesterol and a significant increase in the HDL<sub>2</sub>-cholesterol subfraction, without adverse  
12 effects on fasting glucose concentrations.”<sup>2462</sup> Mori 2000 also states that “[d]espite an increase  
13 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may  
14 be favorable.”<sup>2463</sup> Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori  
15 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the  
16 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away  
17 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for  
18 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,  
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20 <sup>2459</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

21 <sup>2460</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354  
22 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)  
23 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

24 <sup>2461</sup> Mori 2000 at 1092.

<sup>2462</sup> Mori 2000 at 1088.

<sup>2463</sup> Mori 2000 at 1092.

1 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration  
2 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,  
3 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
4 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill  
5 would have sought to combine Mori 2000 with the Lovaza PDR.

6 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it  
7 was known that DHA alone was responsible for the increase in LDL-C levels. Further,  
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
9 has little effect on LDL-C levels.<sup>2464</sup> Defendants identify no other basis upon which a person of  
10 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,  
11 Leigh-Firbank and/or Mori 2000.

12 (ii) The '677 Patent is not Obvious Over the  
13 Omacor PDR/Lovaza PDR, in Combination  
14 with Katayama and/or Matsuzawa, and/or  
15 Takaku, Further in View of Nozaki and/or  
Hayashi, and Further in View of  
Grimsgaard, Mori 2000 and/or Maki

16 With respect to the '677 Patent, Defendants present a combination of nine references:  
17 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering  
18 purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku, further in view of Nozaki  
19 and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."<sup>2465</sup> Defendants  
20 also present charts purporting to assert that an additional 58 references may be combined in order  
21 to render the Claims obvious. Not only do Defendants ignore the improbability that a person of  
22 ordinary skill would combine 58 separate references, they additionally do not identify any

23 <sup>2464</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>2465</sup> Defendants' Joint Invalidation Contentions at 305-06.

1 motivation for combining these references. Although Defendants need not point to an explicit  
2 statement in the prior art motivating the combination of these references, any assertion of an  
3 “apparent reason” to combine must find a basis in the factual record.<sup>2466</sup> Defendants’  
4 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2467</sup>  
5 Defendants’ contentions are no more than an assertion that certain claim elements were known in  
6 the prior art. Throughout their contentions, Defendants’ selectively cite to data points in a  
7 reference without considering other disclosures or even the reference as a whole. Each  
8 reference, however, must be evaluated for all that it teaches.<sup>2468</sup> Accordingly, Defendants fail to  
9 meet their burden to establish *prima facie* obviousness.

10 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method  
11 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the  
12 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR  
13 further do not disclose a method to effect the claimed TG reduction without substantially  
14 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA  
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16 <sup>2466</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2467</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>2468</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the  
2 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose  
3 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375  
4 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500  
5 mg/dL) TG levels. The proposed combinations do not render the independent claim of the '677  
6 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the  
7 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both  
8 generally and the Lovaza package insert specifically) during prosecution.<sup>2469</sup>

9 The analysis of the independent claim of the '677 Patent is incorporated into all asserted  
10 claims that depend from this Claim.

11 (a) A Person of Ordinary Skill Would  
12 Not Have Been Motivated to  
13 Replace the Mixed Fish Oil Active  
Ingredient in Omacor/Lovaza with  
EPA of the Claimed Purity

14 For an invention to be obvious, there must have been an "apparent reason" to make it.  
15 The subject matter of the '677 patent claims would not have been obvious in light of these  
16 references because a person of ordinary skill would not have been motivated to purify EPA or  
17 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
18 levels without an increase in LDL-C levels.

19 (i) Grimsgaard, Katayama,  
20 Matsuzawa and/or Takaku  
Do Not Disclose Purported

21  
22 \_\_\_\_\_  
23 <sup>2469</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").



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2  
3 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the  
4 “known clinical benefits of administering pure EPA - lowering triglycerides without raising  
5 LDL-C.” As discussed in Section V.E.3.c.1.a.i.a.i, incorporated herein by reference, Katayama  
6 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to  
7 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported  
8 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that  
9 the LDL-C results obtained were a clinical benefit.

10 Defendants also rely on Grimsgaard to support their assertion that “administration of  
11 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”<sup>2470</sup> However,  
12 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on  
13 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

14 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA  
15 administered to people with normal triglyceride levels for 7 weeks.<sup>2471</sup> The results from the  
16 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the  
17 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that  
18 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid  
19 supplements, which is consistent with previous studies which “suggested that serum HDL-C is  
20 better maintained with oil rich in DHA than oil rich in EPA.”<sup>2472</sup> Although Grimsgaard states

21  
22 <sup>2470</sup> Defendants’ Joint Invalidity Contentions at 309.

23 <sup>2471</sup> Defendants state in their Joint Invalidity Contentions at 297 that Grimsgaard was conducted in patients with TG  
24 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG  
levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

<sup>2472</sup> Grimsgaard at 654.

1 that EPA may produce a small decrease in serum total cholesterol, it does not specifically  
 2 comment on EPA's effect on LDL-C.

3 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to  
 4 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in  
 5 LDL-C by EPA, as confirmation "that administration of purified DHA results in increased LDL-  
 6 C levels while administration of purified EPA resulted in a decrease in LDL-C levels."<sup>2473</sup> The  
 7 results of Grimsgaard, reproduced below, show that EPA and DHA's impact on LDL-C were the  
 8 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo's  
 9 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to  
 10 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard's  
 11 disclosure highlights the importance of a placebo-controlled study and why results compared  
 12 only to baseline may be misleading. This type of exaggeration and misinterpretation of the  
 13 results published in the prior art is seen throughout the Defendants' invalidity contentions.

14 **TABLE 4**  
 Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>2</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
<b>LDL cholesterol (mmol/L)</b>	<b>4.06 ± 0.86</b>	<b>0.07 ± 0.46</b>	<b>4.06 ± 0.83</b>	<b>-0.08 ± 0.48</b>	<b>4.04 ± 0.98</b>	<b>0.06 ± 0.48</b>	<b>0.10</b>	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>2</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>4</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>5</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>2-5</sup> One-sample t test of difference between baseline and 7 wk: <sup>3</sup> P < 0.001, <sup>4</sup> P < 0.01, <sup>5</sup> P < 0.05.

20 Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential  
 21 effects on lipoprotein and fatty acid metabolism."<sup>2474</sup> However, Grimsgaard does not conclude

23 <sup>2473</sup> Defendants' Joint Invalidity Contentions at 309 n.43.

24 <sup>2474</sup> Grimsgaard at 657.

1 that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that  
2 neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and  
3 DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading  
4 Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of  
5 patients with very-high triglycerides, because net decrease in triglycerides was consistently  
6 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared  
7 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL  
8 cholesterol observed with some n-3 fatty acid supplements.”<sup>2475</sup> Grimsgaard makes no such  
9 statement regarding LDL-C.

10 Defendants cherry-pick results, regardless of whether the effect is found to be statistically  
11 significant compared to placebo, in an attempt to force the studies to support their argument that  
12 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did  
13 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and  
14 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and  
15 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified  
16 DHA results in increased LDL-C levels while administration of purified EPA resulted in a  
17 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did  
18 not have statistically significantly effects on LDL-C compared to placebo.<sup>2476</sup> A person of  
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21 <sup>2475</sup> Grimsgaard at 654.

22 <sup>2476</sup>In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a  
23 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to  
24 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have  
argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make  
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or  
no impact on LDL-C levels.

1 ordinary skill would not draw conclusions regarding differences between EPA and DHA based  
2 on statistically insignificant results.

3 Defendants also rely on Takaku to support their assertion that “clinical benefits of  
4 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the  
5 art.<sup>2477</sup> Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and  
6 safety of Epadel (of undisclosed purity)<sup>2478</sup> based on long-term administration.<sup>2479</sup>

7 A person of ordinary skill would not have concluded based on Takaku that EPA lowers  
8 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly  
9 acknowledges that “only a few subjects were examined” and cautions against drawing a  
10 conclusion “only from the results of the present study.”<sup>2480</sup> Because the study did not include  
11 any placebo control, a person of ordinary skill in the art would understand these reports do not  
12 provide the ability to conclude that the observed lipid effects would have occurred independent  
13 of the drug that is administered. In addition, the study was conducted exclusively in Japanese  
14 patients, and a person of ordinary skill would not have expected the results to be applicable to the  
15 general population.<sup>2481</sup>

16 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a  
17 person of ordinary skill would not have expected the results to be applicable to patients with  
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19 <sup>2477</sup> Defendants’ Joint Invalidity Contentions at 306.

20 <sup>2478</sup> It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by  
21 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),  
Nakamura at 23 (Epadel with purity > 90%).

22 <sup>2479</sup> Takaku at ICOSAPENT\_DFNDT00006834.

23 <sup>2480</sup> Takaku at ICOSAPENT\_DFNDT00006897.

24 <sup>2481</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.”)

1 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because  
2 measurement was not feasible due to “insufficient sample.”<sup>2482</sup> It is possible that patients with  
3 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in  
4 calculating LDL-C levels when triglyceride level is above 400 mg/dL.<sup>2483</sup> Moreover, the study  
5 does not provide different LDL-C graphs based on the baseline triglyceride levels.<sup>2484</sup> Therefore,  
6 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had  
7 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C  
8 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile  
9 throughout the study period, decreasing slightly at times but increasing by more than 8% at other  
10 times.<sup>2485</sup> Because of this volatility, a person of ordinary skill would not be able to conclude  
11 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in  
12 LDL-C, stating only that the fluctuation in LDL-C was not significant.<sup>2486</sup>

13 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA  
14 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has  
15 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the  
16 administration of *fish oil* to hypercholesterolemia patients.”<sup>2487</sup> In contrast, Takaku states merely  
17 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary  
18  
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20 <sup>2482</sup> Takaku at ICOSAPENT\_DFNDT00006884.

21 <sup>2483</sup> See Matsuzawa at ICOSPENT\_DFNDTS00006450.

22 <sup>2484</sup> Takaku at Fig. 13, ICOSAPENT\_DFNDT00006882.

23 <sup>2485</sup> Takaku at Fig. 14, ICOSAPENT\_DFNDT00006883.

24 <sup>2486</sup> Takaku at ICOSAPENT\_DFNDT00006897.

<sup>2487</sup> Takaku at ICOSAPENT\_DFNDT00006897.

1 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study  
2 was attributable to fish oil in general, not EPA specifically.

3 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate  
4 Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other  
5 studies cited by Defendants suggest that EPA increases LDL-C.<sup>2488</sup> Defendants identify no other  
6 basis upon which a person of ordinary skill would have sought to combine the Omacor  
7 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

8 (ii) Nozaki and/or Hayashi  
9 Would Not Have Rendered  
10 the Asserted Claims Obvious

11 Defendants contend that the asserted claims of the '677 patent would have been obvious  
12 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
13 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
14 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
15 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
16 very high TG patient population.

17 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
18 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
19 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
20 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
21 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
22 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
23 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

24 <sup>2488</sup> See, e.g., Rambjor.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
2 patient population were abnormally high and would not have relied upon these results. Further,  
3 the person of skill in the art would not have looked to this patient population to predict the Apo-  
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
6 levels.<sup>2489</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
12 the EPA and the DHA content in the composition that was administered is unknown. A person  
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
15 C were not statistically significant.<sup>2490</sup> Further, the person of skill in the art would not have  
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
21 administered to the very high TG patient population.

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23 <sup>2489</sup> Nozaki at 256.

24 <sup>2490</sup> Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not  
2 placebo controlled. This study would not have been extrapolated to Western populations  
3 because the Japanese diet contains much more fish and has a number of other different attributes.  
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
5 populations. In fact, Defendants' own reference states that the results from studies where the  
6 patient population is exclusively Japanese cannot be generalized to other populations.<sup>2491</sup> The  
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
10 the Japanese respond differently to lipid lowering agents than Westerners.

11 Further, Defendants have failed to offer a purported combination of references as part of  
12 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
13 motivation to combine Nozaki and Hayashi with the other references of their purported  
14 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
15 references.

(iii) Grimsgaard, Mori 2000  
and/or Maki Do Not Disclose  
Purported Knowledge that  
DHA was Responsible for the  
Increase in LDL-C

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that  
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
21 C levels."<sup>2492</sup> Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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23 <sup>2491</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

24 <sup>2492</sup> Defendants' Joint Invalidity Contentions at 308.



1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
2 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”  
3 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
4 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.  
5 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
6 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or  
7 Maki—as in very-high TG patients because patients with higher TG levels had different lipid  
8 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
9 considered fundamentally different from patients with borderline-high or high triglycerides from  
10 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of  
11 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would  
12 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would  
13 substantially increase LDL-C in patients with very high TG levels.

14 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known  
15 that “DHA was responsible for the increase in LDL-C levels.”<sup>2493</sup> The discussion related to  
16 Grimsgaard in Section V.E.3.c.1.a.ii.a.i and Mori 2000 in Section V.E.3.c.1.a.i.a.iii is  
17 incorporated herein by reference.

18 Defendants argue that Maki discloses the administration of purified DHA resulted in the  
19 desired reduction of TGs, but also significantly increased LDL-C levels.<sup>2494</sup> Maki was designed  
20 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with  
21

22 \_\_\_\_\_  
23 <sup>2493</sup> Defendants’ Joint Invalidation Contentions at 306.

24 <sup>2494</sup> Defendants’ Joint Invalidation Contentions at 308-09.

1 below-average levels of HDL-C levels.<sup>2495</sup> The DHA supplemented group was administered  
2 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,  
3 monounsaturated and polyunsaturated fatty acids.<sup>2496</sup> Therefore, Maki demonstrated that when  
4 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average  
5 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is  
6 observed.<sup>2497</sup> However, one cannot attribute the rise in LDL-C solely to DHA, because the  
7 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have  
8 also contributed to the elevation in LDL cholesterol.”<sup>2498</sup> Further, Maki admits that the  
9 “mechanism(s) responsible for the changes in the lipid profile associated with DHA  
10 supplementation are not fully understood.”<sup>2499</sup> Therefore, the results of Maki are inconclusive as  
11 to DHA’s effect alone on LDL-C levels.

12 Defendants mischaracterize the rise in LDL-C associated with the administration of  
13 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-  
14 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in  
15 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol  
16 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of  
17 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level  
18  
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20 <sup>2495</sup> Maki at 190.

21 <sup>2496</sup> Maki at 191.

22 <sup>2497</sup> Maki at 195.

23 <sup>2498</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

24 <sup>2499</sup> Maki at 197.

1 less worrisome.”<sup>2500</sup> Therefore, when one of ordinary skill in the art reviewed all the lipid effects  
2 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was  
3 “less worrisome” because of the “potentially favorable effects on triglycerides, the  
4 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense  
5 particles.”<sup>2501</sup>

6 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
7 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
9 has little effect on LDL-C levels.<sup>2502</sup> Defendants identify no other basis upon which a person of  
10 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,  
11 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

12 (iii) The ‘677 Patent is not Prima Facie Obvious  
13 Over the Omacor PDR/Lovaza PDR, in  
14 Combination with Katayama in View of  
Satoh and/or in View of Satoh or Shinozaki  
in Further View of Contacos

15 With respect to the ‘677 Patent, Defendants present a combination of five references: “the  
16 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering  
17 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in  
18 further view of Contacos.”<sup>2503</sup> Defendants also present charts purporting to assert that an  
19 additional 60 references may be combined in order to render the Claims obvious. Not only do  
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21 <sup>2500</sup> Maki at 197.

22 <sup>2501</sup> Maki at 197.

23 <sup>2502</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>2503</sup> Defendants’ Joint Invalidity Contentions at 306.

1 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate  
2 references, they additionally do not suggest any identify for combining these references.  
3 Although Defendants need not point to an explicit statement in the prior art motivating the  
4 combination of these references, any assertion of an “apparent reason” to combine must find a  
5 basis in the factual record.<sup>2504</sup> Defendants’ unsupported cobbling of selective disclosures  
6 represents hindsight reconstruction.<sup>2505</sup> Defendants’ contentions are no more than an assertion  
7 that certain claim elements were known in the prior art. Throughout their contentions,  
8 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
9 even the reference as a whole. Each reference, however, must be evaluated for all that it  
10 teaches.<sup>2506</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
11 obviousness.

12 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
13 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty  
14 acid compositions or administration period. The Lovaza PDR further does not disclose a method  
15

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16 <sup>2504</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2505</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>2506</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza  
2 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference  
3 would cause a significant increase in LDL-C levels in the very high TG patient population, for  
4 whom the product is indicated. At most, the Lovaza PDR discloses administration of a  
5 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an  
6 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG  
7 levels.

8 Defendants formulate an obviousness argument that relies on Contacos.<sup>2507</sup> However,  
9 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim  
10 element, an “apparent reason” or motivation to combine the elements in the manner claimed,<sup>2508</sup>  
11 or “a reasonable expectation of success”<sup>2509</sup> of achieving the claimed invention.

12 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and  
13 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,  
14 Contacos fails to provide motivation to administer purified EPA to a very high TG patient  
15 population and does not provide any reasonable expectation of success in lowering TG levels in  
16 the very high TG patient population without increasing LDL-C. Contacos also fails to provide  
17 motivation to administer purified EPA to a very high TG patient population and does not provide  
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19 <sup>2507</sup> *Id.*

20 <sup>2508</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 <sup>2509</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

1 any reasonable expectation of success in lowering TG levels in the very high TG patient  
2 population without increasing LDL-C.

3 The proposed combinations do not render the independent claim of the '677 Patent  
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
5 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally  
6 and the Lovaza package insert specifically) during prosecution.<sup>2510</sup>

7 The analysis of the independent claim of the '677 Patent is incorporated into all asserted  
8 claims that depend from this Claim.

9 (a) A Person of Ordinary Skill Would  
10 Not Have Been Motivated to  
11 Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with EPA of  
the Recited Composition

12 For an invention to be obvious, there must have been an "apparent reason" to make it.  
13 The subject matter of the '677 patent claims would not have been obvious in light of these  
14 references because a person of ordinary skill would not have been motivated to purify EPA or  
15 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
16 levels without an increase in LDL-C levels.

17 (i) Katayama, Satoh and/or  
18 Shinozaki Do Not Disclose  
19 Purported Known Clinical  
Benefits of Administering  
Pure EPA

20 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical  
21 benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As

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23 <sup>2510</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").

1 | discussed in Section V.E.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely  
2 | confirms the safety of long term treatment of Epadel and its ability to lower both serum total  
3 | cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone  
4 | discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or  
5 | suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary  
6 | skill view these references as teaching such a benefit for very-high TG patients.

7 |         Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
8 | EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
9 | systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when  
10 | compared to baseline, there was no significant effect when compared to placebo.<sup>2511</sup>

11 | Defendants’ characterization of Satoh as disclosing the lowering of TG levels without increasing  
12 | LDL-C to be a “clinical benefit” is incorrect.<sup>2512</sup> Satoh does not disclose or suggest that the  
13 | LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these  
14 | references as teaching such a benefit for very-high TG patients. As discussed above, one of  
15 | ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500  
16 | mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,  
17 | however, would have expected that fish oils (and other TG lowering agents) would substantially  
18 | increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to  
19 | administer purified EPA to a very high TG patient population and does not provide any  
20 | reasonable expectation of success in lowering TG levels in the very high TG patient population  
21 | without increasing LDL-C.

22 |  
23 | \_\_\_\_\_  
<sup>2511</sup> Satoh at 145.

24 | <sup>2512</sup> Defendants’ Joint Invalidation Contentions at 305.

1 Further, Satoh was a small study conducted in only Japanese patients. This study would  
2 not have been extrapolated to Western populations because the Japanese diet contains much  
3 more fish and has a number of other different attributes. The Japanese consume a higher amount  
4 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference  
5 states that the results from studies where the patient population is exclusively Japanese cannot be  
6 generalized to other populations.<sup>2513</sup> The Japanese diet comprises between 8 and 15 times more  
7 EPA and DHA than typical the typical Western diet. The Western diet typically consists of  
8 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a  
9 person of ordinary skill would understand that the Japanese respond differently to lipid lowering  
10 agents than Westerners.

11 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))  
12 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.  
13 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without  
14 increasing LDL-C to be a "clinical benefit" is incorrect.<sup>2514</sup> Shinozaki says nothing about an  
15 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by  
16 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."<sup>2515</sup> In  
17 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis  
18 upon which a person of ordinary skill would have sought to combine the composition disclosed  
19 in Shinozaki.

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22 <sup>2513</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

23 <sup>2514</sup> Defendants' Joint Invalidity Contentions at 305.

24 <sup>2515</sup> Shinozaki at 107-109.





1 person of ordinary skill in the art would have expected that fish oils (and other TG lowering  
2 agents) would not increase LDL-C substantially in patients with normal to borderline high TG  
3 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in  
4 patients with very high TG levels.

5 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA  
6 was responsible for the increase in LDL-C levels.”<sup>2518</sup> Both Geppert and Kelley administer  
7 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.  
8 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the  
9 independent effects of DHA because it is not clear how much of the supplement’s effects can be  
10 attributed to DHA.<sup>2519</sup> For example, Defendants’ own prior art teaches that changes in fatty acid  
11 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.<sup>2520</sup>

12 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to  
13 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been  
14 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior  
15 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”<sup>2521</sup> Rather than reading  
16 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior  
17 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there  
18 was confusion in the art and it was unclear whether DHA increased LDL-C.

19 A person of ordinary skill would have expected that Geppert’s results would be  
20 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA

21 \_\_\_\_\_  
22 <sup>2518</sup> Defendants’ Joint Invalidation Contentions at 306.

23 <sup>2519</sup> See Mori 2006 at 96.

24 <sup>2520</sup> Maki at 197.

<sup>2521</sup> Geppert at 784.

1 was the only component of fish oil to increase LDL-C. For example, there is no data comparing  
2 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying  
3 explain the mechanism of LDL-C increase.<sup>2522</sup> A person of ordinary skill would have not  
4 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

5 Defendants contend that Kelley shows that DHA was responsible for the increase in  
6 LDL-C.<sup>2523</sup> In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day  
7 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible  
8 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon  
9 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate  
10 therapy.<sup>2524</sup> Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in  
11 context with the other lipid effects reported in the study. Kelley states that:

12 DHA supplementation may lower the risk of CVD by reducing  
13 plasma triacylglycerols; triacylglycerol:HDL; the number of  
14 small, dense LDL particles; and mean diameter of VLDL particles.  
15 An increase was observed in fasting LDL cholesterol, but it  
16 is unlikely this increase is detrimental because no increase was  
17 observed in the overall number of LDL particles; actually, there  
18 was an 11% reduction that was statistically not significant. The  
19 reason LDL cholesterol increased despite no change in LDL  
20 particle number was that the LDL particles were made larger and  
21 hence more cholesterol rich by DHA treatment.<sup>2525</sup>

22 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation  
23 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle  
24 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the

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21 <sup>2522</sup> *Id.*

22 <sup>2523</sup> Defendants’ Joint Invalidity Contentions at 306.

23 <sup>2524</sup> Kelley at 329.

24 <sup>2525</sup> Kelley at 329

1 concentrations of atherogenic lipids and lipoproteins and increased concentrations of  
2 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular  
3 health.”<sup>2526</sup> Rather than concluding that DHA was uniquely responsible for a rise in LDL-C  
4 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely  
5 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with  
6 negative attributes, a person of ordinary skill would understand that the reference taught towards  
7 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400  
8 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the  
9 very high TG patient population to be different in terms of their response to lipid therapy,  
10 including administration of DHA. A person of ordinary skill in the art would have expected that  
11 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with  
12 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a  
13 substantial increase in LDL-C in patients with very high TG levels.

14 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was  
15 known that DHA was responsible for the increase in LDL-C levels.

16 Throughout their contentions, Defendants’ selectively cite to data points in a reference  
17 without considering other disclosures or even the reference as a whole. Each reference,  
18 however, must be evaluated for all that it teaches.<sup>2527</sup> As is the case with Kelley, Defendants use  
19 hindsight to characterize a reference based on LDL-C levels alone without considering the other  
20  
21

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23 <sup>2526</sup> Kelley at 324, 332.

24 <sup>2527</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 lipid effects studied, considered and reported.<sup>2528</sup> The isolated manner in which Defendants  
2 select such data points is not the approach that a person of ordinary skill would have taken at the  
3 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.  
4 A person of ordinary skill would take into consideration the entire disclosure of a reference,  
5 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,  
6 without explanation, the other effects of DHA that a person of ordinary skill would consider.  
7 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a  
8 favorable effect in hypertriglyceridemic patients.

9 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was  
10 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,  
11 without explanation, other studies that demonstrate that DHA decreases or has little effect on  
12 LDL-C levels.<sup>2529</sup> Defendants identify no other basis upon which a person of ordinary skill  
13 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,  
14 Geppert and/or Kelley.

15 (iv) A Person of Ordinary Skill Would Not Have  
16 been Motivated to Find an Omega-3 Fatty  
17 Acid "Therapy that Would Reduce TG  
18 Levels in Patients with TG Levels  $\geq$ 500  
mg/dL Without Negatively Impacting LDL-  
C Levels."

19 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG  
20 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there  
21 was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,

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22 <sup>2528</sup> Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation  
23 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean  
diameters of these particles in fasting and postprandial plasma.").

24 <sup>2529</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels  
2 for very-high TG patients at the time of the invention. A person of ordinary skill in the art  
3 understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and  
4 Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were  
5 available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription  
6 omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly  
7 undesirable side effects—including “flushing” (or reddening of the face and other areas with a  
8 burning sensation) and dyspepsia—that limited their usefulness.<sup>2530</sup> Fibrates were effective at  
9 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG  
10 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an  
11 LDL-C lowering medication such as a statin.<sup>2531</sup> However, the risk of rhabdomyolysis increased  
12 five-fold if fibrates were administered with a statin.<sup>2532</sup> Therefore, physicians were reluctant to  
13 recommend, and patients were hesitant embrace, a combination fibrate/statin course of  
14 treatment.<sup>2533</sup> Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to  
15 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,  
16 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

17 In any event, a person of ordinary skill in the art would have understood that omega 3-  
18 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high  
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20 <sup>2530</sup> See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 <sup>2531</sup> Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”);

22 <sup>2532</sup> See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 <sup>2533</sup> See *Id.*, ¶ 17

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1 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would  
2 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs  
3 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2534</sup>	-20%	+45%
Lovaza/Omacor <sup>2535</sup>	-6%	+45%

7  
8 That Epadel has been approved for decades but not approved for use in the very high TG  
9 patient population prior to the invention of the asserted patents is a real-world reflection of the  
10 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
11 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
12 been countless studies conducted which administer Epadel and report the effects observed.  
13 Although a few studies administer Epadel to a patient population which included a few patients  
14 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
15 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

16 Defendants offer no “apparent reason” to administer EPA as claimed to patients with  
17 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on  
18 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients  
19 with TG levels  $\geq$  500 mg/dL without negatively impacting LDL-C levels.”<sup>2536</sup> Ironically,  
20 Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500 mg/dL but

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22 <sup>2534</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

23 <sup>2535</sup> Chan 2002 I at 2381 (Table 3).

24 <sup>2536</sup> Defendants’ Joint Invalidation Contentions at 308.

1 significantly increases LDL-C--an effect understood to be a consequence of TG reduction and  
2 the increased conversion of VLDL to LDL particles.<sup>2537</sup>

3 It was well known at the time of the invention that omega-3 fatty acids, including both  
4 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant  
5 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3  
6 fatty acids worked in part by inhibiting VLDL production and improving the conversion of  
7 VLDL particles to LDL.<sup>2538</sup> A person of ordinary skill in the art understood that EPA and DHA  
8 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when  
9 discussing the TG-lowering mechanism of omega-3 fatty acids.<sup>2539</sup> The discussion related to the  
10 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and  
11 incorporated herein by reference.

12 In fact, it was well understood that the degree of LDL-C elevation observed with  
13 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG  
14 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels  
15 the most in patients with the highest pretreatment TG levels.<sup>2540</sup> Therefore, a person of ordinary  
16 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct  
17 consequence of lowering triglycerides in patients with TG levels  $\geq 500$  mg/dL. The rise in LDL-  
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19 <sup>2537</sup> See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese  
20 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and  
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in  
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

21 <sup>2538</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
22 decrease in VLDLs after n-3 fatty acid treatment”)

23 <sup>2539</sup> Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*  
24 *Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

<sup>2540</sup> See Bays 2008 Rx Omega-3 p. 402.



1 C was often offset by concurrent treatment with statins.<sup>2541</sup> The safety and efficacy of using  
2 prescription omega-3 in combination with a statin has been well-established.<sup>2542</sup>

3 Although an increase in LDL-C was generally observed when omega-3 fatty acids were  
4 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a  
5 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.

6 Therefore, the final LDL-C concentration may still be in the normal range.<sup>2543</sup> Furthermore, it  
7 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>2544</sup>

8 In two pivotal studies in very-high TG patients, both of which used prospective,  
9 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL  
10 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).<sup>2545</sup> Correspondingly, prescription  
11 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.<sup>2546</sup> Therefore,  
12 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can  
13 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net  
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15 <sup>2541</sup> See Harris 2008 at 14, McKenney at 722.

16 <sup>2542</sup> McKenney at 722-23.

17 <sup>2543</sup> See Westphal at 918, Harris 1997 at 389.

18 <sup>2544</sup> See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals  
with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester  
transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he  
19 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-  
high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the  
20 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute  
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this  
21 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty  
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in  
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by  
22 decreased non-HDL-C levels (TC minus HDL-C”).

23 <sup>2545</sup> McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 <sup>2546</sup> McKenney 2007 at 722 (see Fig. 1).

1 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in  
2 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also  
3 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the  
4 number of small, dense LDL particles to larger LDL particles.<sup>2547</sup> Lovaza/Omacor “adversely  
5 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration  
6 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”<sup>2548</sup>  
7 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3  
8 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not  
9 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention  
10 of [coronary heart disease].”<sup>2549</sup>

11 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at  
12 the time of the claimed inventions would have been motivated to find a therapy that would  
13 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting  
14 LDL-C levels,”<sup>2550</sup> one of ordinary skill in the art at the time of the invention understood that the  
15 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with  
16 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to  
17 increase in very-high TG patients, and in some instances the rise was not concerning because  
18 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final  
19 concentration would still be in the normal range. When LDL-C levels increased beyond what  
20 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

21 \_\_\_\_\_  
22 <sup>2547</sup> McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 <sup>2548</sup> Stalenhoef at 134.

24 <sup>2549</sup> Harris 1997 at 389.

<sup>2550</sup> Defendants’ Joint Invalidation Contentions at 307-08.

1 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of  
2 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to  
3 identify any other basis upon which a person of ordinary skill would have been motivated to find  
4 a therapy that would reduce TG levels in patients with very-high TG levels without negatively  
5 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood  
6 that EPA therapy would *not* reduce Apo-B<sup>2551</sup> (which is a reflection of total atherogenic  
7 lipoproteins)<sup>2552</sup> in very high TG patients, and accordingly would not have been motivated to  
8 administer the claimed EPA composition to the very high TG patient population.

9 Defendants make the conclusory allegation that “routine optimization” by a person of  
10 ordinary skill would yield the claimed invention.<sup>2553</sup> Defendants, however, have offered no  
11 explanation to support that allegation and they further fail to establish any of the required criteria  
12 of “routine optimization” or the prerequisites to this argument. They also fail to provide any  
13 factual detail to support their allegation and they fail to link the allegation to any particular claim  
14 or claim element. Defendants mere allegation constitute an improper placeholder to later  
15 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,  
16 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the  
17 combinations alleged by Defendants and, for the same reasons, it would not be routine to  
18 combine such references. Where, for example, defendants argue that it would be routine to go  
19 from the high TG patient population to the very high TG patient population, they provide no  
20 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

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<sup>2551</sup> *see* Section V.O.

23 <sup>2552</sup> *see* Section III.

24 <sup>2553</sup> *See, e.g.*, Defendants’ Joint Invalidity Contentions at 303, 317, and 333.

1 would have understood these patient populations to be distinct with different impacts of lipid  
2 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would  
3 not have considered the dosage modification suggested by defendants to be routine; Defendants'  
4 argument to the contrary represents hindsight bias.

5 In addition, a person of ordinary skill would have no motivation to combine these  
6 references because EPA would have been expected to have same result as the mixture of EPA  
7 and DHA used in Lovaza/Omacor.

8 (v) A Person of Ordinary Skill Would Not Have  
9 Had a Reasonable Expectation of Success  
10 with the Combinations Defendants  
11 Hypothesize

12 Defendants provide no evidence that a person of ordinary skill would have had a  
13 reasonable expectation of successfully obtaining the claimed invention—a method of reducing  
14 triglycerides in a subject having very-high triglyceride levels by administering EPA of the  
15 recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by  
16 combining the references cited by defendants. For a particular combination of references, there  
17 must be a reasonable expectation that the combination will produce the claimed invention. In  
18 this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with  
19 very-high TG levels.<sup>2554</sup> A person of ordinary skill would have expected EPA, like  
20 Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG  
21 patient population. As discussed in Section III and above, it was well known that TG-lowering

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22 <sup>2554</sup> As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to  
23 have the same TG lowering mechanism and would have further understood that the increase in LDL-C  
24 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of  
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar  
fashion to Lovaza or DHA alone.

agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but caused significant increases in LDL-C levels for patients with very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to expect anything to the contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2555</sup>	-20%	+45%
Lovaza/Omacor <sup>2556</sup>	-6%	+45%

Accordingly, a person of ordinary skill would *not* have a reasonable expectation of success in achieving a reduction in TG levels without substantially increasing LDL-C in patients with very-high TG levels.<sup>2557</sup>

Defendants’ position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to patients with very high triglyceride levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that Defendants’ provide no evidence that anyone thought to administer Epadel.<sup>2558</sup> Epadel was available for many years prior to the invention of the ’677 patent, to patients with very-high TGs as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,

<sup>2555</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

<sup>2556</sup> Chan 2002 I at 2381 (Table 3).

<sup>2557</sup> Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall effect on lipid parameters, teaching away from this combination.

<sup>2558</sup> Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of  
2 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by  
3 Defendants are directed to the use of purified EPA in the very-high TG population.

4 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
5 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
6 countless studies conducted which administer Epadel and report the effects observed. Although  
7 a few studies administer Epadel to a patient population which included a few patients with TG  
8 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
9 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
10 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
11 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
12 triglycerides.

13 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients  
14 with borderline-high/high TG, it would have been obvious to try administering purified ethyl  
15 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants  
16 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of  
17 2.7 grams of purified EPA to patients with >500 mg/dL TG by Matsuzawa.<sup>2559</sup> Defendants'  
18 contentions are no more than a demonstration that certain claim elements was known in the prior  
19 art and demonstrates impermissible hindsight reconstruction.<sup>2560</sup> As is reflected in Table 4 of  
20 Grimsgaard, the study authors found no difference between the DHA, EPA, and control in terms  
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22 <sup>2559</sup> Defendants' Joint Invalidation Contentions at 310.

23 <sup>2560</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
24 KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.").

of LDL-C levels. Defendants use hindsight to argue that, despite EPA and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably, none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

TABLE 4  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>3</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>3</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>4</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>2</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>3-5</sup> One-sample *t* test of difference between baseline and 7 wk: <sup>3</sup>  $P < 0.001$ , <sup>4</sup>  $P < 0.01$ , <sup>5</sup>  $P < 0.05$ .

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.

1 To the extent that Defendants’ arguments are based on results that are not statistically  
2 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not  
3 draw conclusions from these statistically insignificant differences. Indeed, the standard  
4 deviation for the changes reported is greater than the value of the change itself.

5 Defendants argue that it would have been obvious to try administering purified ethyl EPA  
6 to patients with very-high TG levels with a reasonable expectation of success. However, the  
7 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-  
8 try” proves that the claimed invention was obvious where the prior art did not suggest what to  
9 try.<sup>2561</sup> Rather than there being a limited number of options, the state of the art provided a  
10 plethora of compositions and administration protocols associated with multiple kinds of TG-  
11 lowering therapies.<sup>2562</sup> There were not a finite number of options for a person of ordinary skill  
12 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient  
13 population.

14 Defendants argue that a person of ordinary skill at the time of the invention, based on  
15 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone  
16 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to  
17 no impact on LDL-C levels.<sup>2563</sup> However, that statement does not conform with what was  
18 known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high  
19 TG patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor  
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<sup>2561</sup> See *Sanofi*, 748 F.3d at 1360–61.

23 <sup>2562</sup> See *supra* Section III.

24 <sup>2563</sup> Defendants’ Joint Invalidity Contentions at 309.



1 were both known to have little or no effect on LDL-C in patients with borderline-high/high TG  
2 levels.

3 With the lack of any reasonable expectation of success, Defendants argue that their  
4 proposed combination amounts to a simple substitution of one known element for another, and  
5 that that these changes yield predictable results.<sup>2564</sup> Such an argument, however, represents pure  
6 and impermissible hindsight bias and further does not consider that reasons for which a person of  
7 ordinary skill would not be motivated to combine these references and affirmatives ways in  
8 which the art taught away from these combinations.

9 (b) Defendants Have Not Shown It Would Have Been  
10 Obvious to Administer Purified EPA in the Dosing  
Regimen Recited in the Claims

11 (i) The '677 Patent is not Obvious Over WO  
12 '118 or WO '900, in Combination with the  
Lovaza PDR, and Further in View of Leigh-  
13 Firbank and/or Mori 2000

14 With respect to the '677 Patent, Defendants present a combination of five references:  
15 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the  
16 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."<sup>2565</sup> Defendants also  
17 present charts arguing that an additional 61 references may be combined in order to render the  
18 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill  
19 would combine 61 separate references, they additionally do not identify any motivation for  
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23 <sup>2564</sup> Defendants' Joint Invalidation Contentions at 311.

24 <sup>2565</sup> Defendants' Joint Invalidation Contentions at 312-13.

1 combining these references.<sup>2566, 2567</sup> Although Defendants need not point to an explicit statement  
2 in the prior art motivating the combination of these references, any assertion of an “apparent  
3 reason” to combine must find a basis in the factual record.<sup>2568</sup> Defendants’ unsupported cobbling  
4 of selective disclosures represents hindsight reconstruction.<sup>2569</sup> Defendants’ contentions are no  
5 more than an assertion that certain claim elements were known in the prior art. Throughout their  
6 contentions, Defendants’ selectively cite to data points in a reference without considering other  
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
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10 <sup>2566</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more the references cited in  
11 V.B.3 and 4, including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi, Katayama,  
12 Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki,  
13 Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-  
Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a person of  
ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to meet the  
disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these  
references. *See* Defendants’ Joint Invalidity Contentions at 312.

14 <sup>2567</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
15 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
16 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person  
having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 303.

17 <sup>2568</sup> *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point  
20 “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation  
to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties  
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.  
21 Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*  
*facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and  
22 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art  
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>2569</sup> *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.<sup>2570</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
2 obviousness.

3 WO '118 is directed at the composition containing EPA for the purpose of preventing the  
4 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118  
5 is directed, "in particular, [to] preventing occurrence of cardiovascular events in  
6 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the  
7 risk of the cardiovascular events."<sup>2571</sup> Contrary to Defendants' assertion that WO '118 discloses  
8 "the administration of 4 g of pure EPA with no DHA,"<sup>2572</sup> WO '118 fails to disclose the claimed  
9 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive  
10 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified  
11 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction  
12 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of  
13 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in  
14 the disclosed composition.<sup>2573</sup>

15 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target  
16 population of the claimed invention. The asserted claims are directed to persons with severe  
17 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only  
18 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.<sup>2574</sup> WO  
19 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

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20 <sup>2570</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>2571</sup> WO '118 at 9.

22 <sup>2572</sup> Defendants' Joint Invalidation Contentions at 313.

23 <sup>2573</sup> WO '118 at 22-23.

24 <sup>2574</sup> WO '118 at 8.

1 patients with borderline-high to high TG levels, since the primary goal for patients with very-  
2 high TG is to prevent acute pancreatitis by decreasing TG levels.<sup>2575</sup>

3 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the  
4 effectiveness of the substances for treating hypertriglyceridemia.<sup>2576</sup> WO '118 states that  
5 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-  
6 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +  
7 DHA-E) are not particularly limited as long as intended effects of the present invention are  
8 attained.”<sup>2577</sup> It further states that “the composition is preferably the one having a high purity of  
9 EPA-E and DHA-E.”<sup>2578</sup> Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C,  
10 Apo-B, or Lp-PLA2.

11 WO '900 is directed to a process for producing purified EPA from a culture of micro-  
12 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels  
13 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed  
14 pharmaceutical composition with the specified dosage or administration period, or the claimed  
15 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900  
16 only discloses the method of producing purified EPA for therapeutic use, it does not teach  
17 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient  
18 population or method of treatment.

19  
20  
21 <sup>2575</sup> See Section III.

22 <sup>2576</sup> WO '118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective  
component”).

23 <sup>2577</sup> WO '118 at 22-23.

24 <sup>2578</sup> WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It  
2 lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one  
3 of them.<sup>2579</sup> Moreover, WO '900 does not teach the desired effect of EPA other than  
4 commenting generally that it “may promote health and ameliorate or even reverse the effects of a  
5 range of common diseases.”<sup>2580</sup> It has no discussion, for example, on any TG-lowering effect of  
6 EPA. Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the  
7 *specific* undesired effect of DHA or other impurities it is trying to prevent other than  
8 commenting generally that “the desired effects of EPA may be limited or reversed” by them.<sup>2581</sup>  
9 It has no discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claim of the '677 Patent  
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package  
13 insert specifically) during prosecution.<sup>2582</sup>

14 The analysis of the independent claim of the '677 patent is incorporated into all asserted  
15 claims that depend from this Claim.

16 (a) Leigh-Firbank and Mori 2000 Do  
17 Not Disclose Purported Knowledge  
18  
19

20 <sup>2579</sup> See, e.g., '900 Pub. at 16-17.

21 <sup>2580</sup> '900 Pub. at 5.

22 <sup>2581</sup> '900 Pub. at 39.

23 <sup>2582</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 that DHA was Responsible for the  
2 Increase in LDL-C

3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known  
5 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-  
6 C levels as evidenced by Leigh-Firbank or Mori 2000.”<sup>2583</sup>

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with  
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need  
9 not point to an explicit statement in the prior art motivating the combination of these references,  
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>2584</sup>

11 Defendants’ unsupported cobbling of selective disclosures represents hindsight  
12 reconstruction.<sup>2585</sup> Defendants’ contentions are no more than an assertion that certain claim  
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to  
14 establish *prima facie* obviousness.

15  
16 <sup>2583</sup> Defendants’ Joint Invalidity Contentions at 313.

17 <sup>2584</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2585</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that  
2 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank  
3 and Mori 2000 in Section V.E.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank  
4 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and  
5 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does  
6 not offer any disclosure regarding the effect of EPA and DHA separately or gain any  
7 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000  
8 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is  
9 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation  
10 to combine with WO ‘118 or WO ‘900. Engaging in hindsight bias, Defendants ignore, without  
11 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants  
12 fail to identify any other basis upon which a person of ordinary skill would have sought to  
13 combine Mori 2000 with the Lovaza PDR.

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants  
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little  
17 effect on LDL-C levels.<sup>2586</sup> Defendants identify no other basis upon which a person of ordinary  
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or  
19 Mori.

- 20 (ii) The ‘677 Patent is not Obvious Over WO  
21 ‘118, WO ‘900, Grimsgaard, Mori 2000  
22 and/or Maki in Combination with the  
23 Omacor PDR/Lovaza PDR, and Further in

24 <sup>2586</sup> See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '677 Patent, Defendants present a combination of nine references:

“WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku.”<sup>2587</sup> Defendants also present charts arguing that an additional 56 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 56 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>2588</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2589</sup> Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

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<sup>2587</sup> Defendants’ Joint Invalidity Contentions at 313.

<sup>2588</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2589</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).



1 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
2 even the reference as a whole. Each reference, however, must be evaluated for all that it  
3 teaches.<sup>2590</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
4 obviousness.

5 The discussion related to WO ‘118 and WO ‘900 in Section V.E.3.c.1.b.i is incorporated  
6 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section  
7 V.E.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and  
8 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”  
9 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the  
10 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to  
11 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other  
12 basis upon which a person of ordinary skill would have sought to combine the composition  
13 disclosed in Grimsgaard or Mori 2000.

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art  
15 to use EPA as described in WO ’118, WO ‘900, Grimsgaard or Mori 2000 in the treatment  
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their  
17 assertions fail to provide a motivation for combining the references.<sup>2591</sup> Although Defendants  
18 need not point to an explicit statement in the prior art motivating the combination of these  
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual  
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22 \_\_\_\_\_  
23 <sup>2590</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>2591</sup> Defendants’ Joint Invalidity Contentions at 313.

1 record.<sup>2592</sup> Defendants’ assertions related to motivation are insufficient,<sup>2593</sup> and accordingly  
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or  
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference  
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the  
6 manner claimed,<sup>2594</sup> or “a reasonable expectation of success”<sup>2595</sup> of achieving the claimed  
7 invention. Therefore, Defendants should be precluded from relying on this these references.

8 As discussed above in Section V.E.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only  
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both  
10

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11  
12 <sup>2592</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
13 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
14 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
15 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
16 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
17 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
18 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
19 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
20 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
21 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
22 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
23 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

17 <sup>2593</sup> For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating  
18 hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any  
19 basis for that statement. While the paragraph associated with that statement makes assertions regarding the  
20 disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO  
21 ’118. See Defendants’ Joint Invalidity Contentions at 314.

20 <sup>2594</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
23 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 <sup>2595</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

1 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer  
2 purified EPA to the very high TG patient population and do not provide any reasonable  
3 expectation of success in lowering TG levels in the very high TG patient population without  
4 increasing LDL-C. As discussed above in Section V.E.3.c.1.a.ii.a.i, Takaku candidly  
5 acknowledges that “only a few subjects were examined” and cautions against drawing a  
6 conclusion “only from the results of the present study.”<sup>2596</sup> Further, the study did not include any  
7 placebo control, therefore, a person of ordinary skill in the art would understand these reports do  
8 not provide the ability to conclude that the observed lipid effects would have occurred  
9 independent of the drug that is administered. In addition, the study was conducted exclusively in  
10 Japanese patients, and a person of ordinary skill would not have expected the results to be  
11 applicable to the general population.<sup>2597</sup>

12 The proposed combination does not render the independent claim of the '677 Patent  
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and  
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.<sup>2598</sup>

16 The analysis of the independent claim of the '677 patent is incorporated into all asserted  
17 claims that depend from this Claim.

18 (a) Grimsgaard, Mori 2000 and/or Maki  
19 Do Not Disclose Purported  
20 Knowledge that DHA was

21 <sup>2596</sup> Takaku at ICOSAPENT\_DFNDT00006897.

22 <sup>2597</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.”)

23 <sup>2598</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).

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2  
3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known  
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is  
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or  
7 Maki.”<sup>2599</sup>

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose  
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,  
10 Mori 2000 and/or Maki in Section V.E.3.c.1.a.ii.a.iii is incorporated herein by reference. A  
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA  
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,  
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although  
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not  
15 disclose administration of DHA to the requisite patient population and teaches that DHA is  
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,  
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
18 would consider. Most controlled studies in patients with normal to high baseline TG levels  
19 indicated that DHA had little or no effect on LDL-C.<sup>2600</sup> Therefore, a person of ordinary skill  
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline  
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 <sup>2599</sup> Defendants’ Joint Invalidity Contentions at 314.

23 <sup>2600</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG  
2 levels, a significant increase in LDL-C is observed.<sup>2601</sup> However, one of ordinary skill in the art  
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.<sup>2602</sup>  
4 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
8 has little effect on LDL-C levels.<sup>2603</sup> Defendants identify no other basis upon which a person of  
9 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,  
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

11 (iii) A Person of Ordinary Skill Would Not Have  
12 Been Motivated to Administer Purified EPA  
13 in the Treatment Regimen Recited in the  
14 Claims

14 For an invention to be obvious, there must have been an “apparent reason” to make it.  
15 Defendants assert that a “person of ordinary skill in the art would have been motivated to  
16 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to  
17 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>2604</sup> However, as  
18 set forth below, Defendants fail to address why a person of ordinary skill in the art would have  
19 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

20 \_\_\_\_\_  
<sup>2601</sup> Maki at 195.

21 <sup>2602</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*  
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A  
23 number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated  
24 fat and cholesterol, both of which are known to elevate LDL-C.”).

<sup>2603</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

<sup>2604</sup> Defendants’ Joint Invalidity Contentions at 314.

1 greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering  
2 triglycerides *without increasing LDL-C levels*.

3 Indeed, a person of ordinary skill in the art would have understood that omega 3-fatty  
4 acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG  
5 patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not  
6 have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without  
7 increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2605</sup>	-20%	+45%
Lovaza/Omacor <sup>2606</sup>	-6%	+45%

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9  
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11  
12 That Epadel has been approved for decades but not approved for use in the very high TG  
13 patient population prior to the invention of the asserted patents is a real-world reflection of the  
14 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
15 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
16 been countless studies conducted which administer Epadel and report the effects observed.  
17 Although a few studies administer Epadel to a patient population which included a few patients  
18 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
19 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

20 Defendants further argue that the disclosure in WO '118 would combine with the prior art  
21 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to

22 \_\_\_\_\_  
23 <sup>2605</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>2606</sup> Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118  
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-  
3 purified ethyl-EPA.”<sup>2607</sup> Both of the “reasons” identified by Defendants are false.

4       Regarding Defendants’ first reason, that “products containing DHA were reported to  
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in  
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on  
7 LDL-C.<sup>2608</sup> Therefore, a person of ordinary skill would not have concluded that DHA increases  
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,  
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,  
10 while EPA does not.”<sup>2609</sup> First, Leigh-Firbank cannot comment on the effect of EPA and DHA  
11 alone because it did not administer EPA and DHA separately.<sup>2610</sup> A person of ordinary skill  
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect  
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA  
14 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with  
15 other saturated and polyunsaturated fatty acids.<sup>2611</sup> Therefore, a person of ordinary skill would  
16 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear  
17 how much of the supplement’s effects can be attributed to DHA.<sup>2612</sup> Kelley does not show that

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<sup>2607</sup> Defendants’ Joint Invalidity Contentions at 314-15.

20 <sup>2608</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
21 controlled, found an increase in LDL-C after DHA administration.

22 <sup>2609</sup> Defendants’ Joint Invalidity Contentions at 319.

23 <sup>2610</sup> The discussion related to Leigh-Firbank in Section V.A.3.c.1.a.i.a.iii is incorporated herein by reference.

24 <sup>2611</sup> The discussion related to Kelley in Section V.A.3.c.1.a.iii.a.ii is incorporated herein by reference.

<sup>2612</sup> See Mori 2006 at 96.

1 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a  
2 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase  
3 was induced by fibrate therapy.<sup>2613</sup> Kelley specifically teaches that the increase in LDL-C  
4 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel  
5 increase in overall LDL particle number. Rather than concluding that DHA was uniquely  
6 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to  
7 disclose that DHA had uniquely beneficial cardioprotective effects.<sup>2614</sup> Finally, Theobald also  
8 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for  
9 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by  
10 7% when compared to placebo. However, the DHA composition that was administered in  
11 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,  
12 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA  
13 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it  
14 impossible to determine whether or how much of the supplement’s effects can be attributed to  
15 DHA.<sup>2615</sup> Contrary to Defendants’ assertion that there was “a reported advantage to using EPA  
16 vs. DHA in hypertriglyceridemic subjects,”<sup>2616</sup> there was no known advantage to using EPA vs.  
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately  
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after  
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20 <sup>2613</sup> Kelley at 329.

21 <sup>2614</sup> Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”  
and that “DHA supplementation may improve cardiovascular health.”)

23 <sup>2615</sup> See Mori 2006 at 96.

24 <sup>2616</sup> Defendants’ Joint Invalidity Contentions at 314.



1 EPA supplementation.”<sup>2617</sup> In addition, a person of ordinary skill would have recognized any  
2 impact of DHA reported by the study to be applicable to EPA because they would have  
3 understood these substances to function by the same mechanism. Furthermore, as discussed  
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in  
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients  
6 because patients with higher TG levels had different lipid responses compared to patients with  
7 lower TG levels.

8           Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in  
9 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”  
10 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been  
11 well documented.<sup>2618</sup> Lovaza/Omacor has been shown to reduce the risk for cardiovascular  
12 death plus nonfatal myocardial infarction and nonfatal stroke.<sup>2619</sup> Omega-3 fatty acids have been  
13 shown to exert cardioprotective effects in both primary and secondary coronary heart disease  
14 prevention trials.<sup>2620</sup> Omega-3 fatty acids were known to reduce TG concentration, have  
15 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure  
16 and/or reduce heart rate.<sup>2621</sup>

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19 <sup>2617</sup> Mori 2000 at 1092.

20 <sup>2618</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA  
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 <sup>2619</sup> See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,  
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

22 <sup>2620</sup> Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,  
197 Atherosclerosis 12, 13 (2008) (“Harris 2008”).

23 <sup>2621</sup> Harris 2008 at 13.

1 Defendants argue that a “person of ordinary skill in the art would have appreciated the  
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce  
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of  
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA-E of WO ‘118.”<sup>2622</sup> As  
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA  
6 and Lovaza/Omacor have been well documented.<sup>2623</sup>

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart  
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that  
9 DHA is *more* cardioprotective than EPA.<sup>2624</sup> This study found that “depressed levels of long-  
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary  
11 heart disease events.”<sup>2625</sup> Further, the study found that DHA levels, with or without EPA, were  
12 significantly lower in fatal endpoints.<sup>2626</sup> This study suggests that DHA is preferable to EPA—  
13 thus teaching away from the claimed invention.<sup>2627</sup> Defendants rely on hindsight bias to argue  
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA  
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16 <sup>2622</sup> Defendants’ Joint Invalidity Contentions at 315.

17 <sup>2623</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA  
18 and CHD risk.”) (“Harris 2007”).

19 <sup>2624</sup> Harris 2007 at 8.

20 <sup>2625</sup> *Id.*

21 <sup>2626</sup> Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all  
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 <sup>2627</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of  
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the  
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*  
*Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs.,*  
*Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the  
prior art ... is strong evidence of nonobviousness.”).

1 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA  
2 was *more* cardioprotective than EPA.

3 Defendants argue that the following claim elements were known: the administration of  
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the  
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to  
6 patients with high and very high TG levels who were not receiving concurrent lipid altering  
7 therapy, and the dose of 4g/day and 12-week regimen.<sup>2628</sup> Defendants then argue that the “only  
8 question is whether one skilled in the art would have been motivated to use the DHA-free,  
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at  
10 least 500 mg/dL as part of the claimed dosage regimen.”<sup>2629</sup>

11 Defendants’ contentions are no more than a recitation that certain claim elements were  
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight  
13 reconstruction.<sup>2630</sup> Notably, Defendants *do not* assert that a person of ordinary skill would have  
14 known that purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL),  
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,<sup>2631</sup>  
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a  
17 number of prior art references disclosed the administration of purified EPA to patients with  
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<sup>2628</sup> Defendants’ Joint Invalidity Contentions at 316-17.

21 <sup>2629</sup> Defendants’ Joint Invalidity Contentions at 317.

22 <sup>2630</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 <sup>2631</sup> Nakamura, Matsuzawa, and Takaku.

1 triglyceride levels > 500 mg/dL.”<sup>2632, 2633</sup> The disclosures of Nakamura (one patient), Matsuzawa  
2 (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support  
3 for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a  
4 person of ordinary skill in the art would *not* understand these references to relate to the use of  
5 EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any  
6 conclusions regarding these references in terms of the very high TG patient population. In  
7 Nakamura, one patient had a baseline TG level > 500 mg/dL.<sup>2634</sup> However, the mean baseline  
8 TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the  
9 other patients was well below 500 mg/dL.<sup>2635</sup> In Matsuzawa, three patients had TG levels  
10 between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.<sup>2636</sup> Based on this  
11 disclosure, only one patient definitively had a baseline TG level  $\geq$  500 mg/dL. Further, this one  
12 patient was excluded when analyzing the lipid impact because he was a “heavy drinker” and the  
13 “effect of alcohol made it impossible to assess triglyceride levels.”<sup>2637</sup> In Takaku, three patients  
14 had baseline TG levels above 500 mg/dL.<sup>2638</sup> However, the mean baseline TG level for all  
15 patients was 245 mg/dL.<sup>2639</sup> Indeed, the mean baseline TG level of the patients in all three

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17 <sup>2632</sup> Defendants’ Joint Invalidity Contentions at 316.

18 <sup>2633</sup> Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500  
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually  
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumura specifically  
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 <sup>2634</sup> Nakamura at 23, Table 1.

23 <sup>2635</sup> Nakamura at 23, Tables 1 and 2.

24 <sup>2636</sup> *Id.* at 23.

<sup>2637</sup> *Id.* at 10.

<sup>2638</sup> Takaku at ICOSAPENT\_DFNDTS00006895.

<sup>2639</sup> Takaku at ICOSAPENT\_DFNDTS00006875.

1 studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected  
2 the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of  
3 these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations  
4 because the Friedewald's Equation cannot be used for patients with triglyceride levels  $\geq$  400  
5 mg/dL.<sup>2640</sup> Defendants have failed to identify all of the claimed elements and fail to provide  
6 motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of  
7 patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated  
9 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the  
10 known TG-lowering effects of highly-purified EPA-E."<sup>2641</sup> This argument is flawed. The prior  
11 art demonstrates a wide range of administration periods utilized in different clinical studies. For  
12 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in  
13 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.  
14 Given the large number of choices of administration periods disclosed in prior art, Defendants  
15 have not shown that a person of ordinary skill would not have been motivated to administer  
16 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

17 Moreover, a person of ordinary skill would not have been motivated to administer highly-  
18 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as  
19 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood  
20 triglycerides.<sup>2642</sup> In fact, Defendants acknowledge in their Joint Invalidation Contentions that

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22 <sup>2640</sup> See Matsuzawa at ICOSAPENT\_DFNDTS00006450.

23 <sup>2641</sup> Defendants' Joint Invalidation Contentions at 317.

24 <sup>2642</sup> Mori 2006 at 98.

1 “DHA and EPA were both known to comparably reduce triglycerides, independently of one  
2 another.”<sup>2643</sup> Data from some studies even suggested that DHA or fish oil may reduce  
3 triglyceride more effectively than EPA.<sup>2644</sup> Therefore, a person of ordinary skill would not have  
4 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination  
5 of EPA and DHA (such as Lovaza) for 12 weeks.

6 Defendants argue that a “person of ordinary skill in the art also would have been  
7 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant  
8 reduction in TG . . . that was achieved in six weeks of treatment,” citing Mori 2000.<sup>2645</sup> This  
9 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with  
10 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to  
11 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

12 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have  
13 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such  
14 as Lovaza).

15 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses  
16 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of  
17 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a  
18 dose of 4 g/day rather than a lower dose.”<sup>2646</sup> A person of ordinary skill would not have relied  
19 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,  
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21 <sup>2643</sup> Defendants’ Joint Invalidation Contentions at 321.

22 <sup>2644</sup> Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor  
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was  
23 grater with DHA supplementation than EPA supplementation).

24 <sup>2645</sup> Defendants’ Joint Invalidation Contentions at 317.

<sup>2646</sup> Defendants’ Joint Invalidation Contentions at 317.

1 because these studies were not designed to determine the effect of dose on the degree of TG  
2 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower  
3 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

4 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood  
5 triglycerides.<sup>2647</sup> Therefore, a person of ordinary skill would not have been motivated to  
6 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of  
7 EPA and DHA (such as Lovaza).

8 Defendants further argue that a “person of ordinary skill in the art would have also been  
9 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with  
10 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much  
11 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito  
12 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”<sup>2648</sup> This argument is  
13 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a  
14 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have  
15 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3  
16 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline  
17 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a  
18 greater decrease in TG levels, in the very high TG patient population, would lead to a greater  
19 increase in LDL-C levels.

20 Defendants contend that a “person of ordinary skill in the art would have been motivated  
21 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a

22 \_\_\_\_\_  
23 <sup>2647</sup> See Section III.

24 <sup>2648</sup> Defendants’ Joint Invalidity Contentions at 317-18.

1 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to  
2 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”<sup>2649</sup> Defendants first  
3 support this argument by asserting that a person of ordinary skill in the art would have known  
4 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is  
5 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA  
6 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,  
7 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in  
8 V.B.4. and 5” to support this proposition,<sup>2650</sup> however these references do not disclose or suggest  
9 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very  
10 high TG patients.<sup>2651</sup>

11 Defendants next argue again that DHA was known to be responsible for the increase in  
12 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of  
13 ordinary skill would understand that both EPA and DHA function similarly, and that both would  
14 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would  
15 increase LDL-C levels in patients with very high TGs.

16 Defendants argue that a person of ordinary skill in the art “would have known that an  
17 increase in LDL-C was an adverse health effect to be avoided.”<sup>2652</sup> While an increase in LDL-C  
18 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that  
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<sup>2649</sup> Defendants’ Joint Invalidation Contentions at 319.

22 <sup>2650</sup> Defendants’ Joint Invalidation Contentions at 319.

23 <sup>2651</sup> *See* Section IV.

24 <sup>2652</sup> Defendants’ Joint Invalidation Contentions at 321.



1 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3  
2 fatty acids generally, was related to increased conversion of VLDL to LDL particles.<sup>2653</sup>

3 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the  
4 art would have been motivated, with a reasonable expectation of success, to administer a highly-  
5 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in  
6 LDL-C with DHA.”<sup>2654</sup> However, a person of ordinary skill in the art expected an increase in  
7 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time  
8 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant  
9 decrease in the production of VLDL particles and a significant increase in the conversion of  
10 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by  
11 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.<sup>2655</sup> A  
12 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering  
13 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering  
14 mechanism of omega-3 fatty acids.<sup>2656</sup> The discussion related to the TG-lowering mechanism of  
15 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

16 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*

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20 <sup>2653</sup> See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription  
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly  
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride  
23 levels when given prescription omega-3 therapy”); Chan 2003.

24 <sup>2654</sup> Defendants’ Joint Invalidity Contentions at 321.

<sup>2655</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”).

<sup>2656</sup> Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

1 reduce Apo-B<sup>2657</sup> (which is a reflection of total atherogenic lipoproteins)<sup>2658</sup> in very high TG  
2 patients, and accordingly would not have been motivated to administer the claimed EPA  
3 composition to the very high TG patient population.

4 Accordingly, a person of ordinary skill would not have been motivated to combine WO  
5 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and  
6 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not  
7 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-  
8 Firbank and/or Mori 2000.

9 (iv) A Person of Ordinary Skill Would Not Have  
10 Had a Reasonable Expectation of Success  
11 with the Combinations Defendants  
Hypothesize

12 Defendants contend that a “person of ordinary skill in the art would have been motivated  
13 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal  
14 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>2659</sup>

15 Defendants also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . .  
16 would have given a person of ordinary skill in the art a reasonable expectation of successfully  
17 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in  
18 these subjects relative to baseline or placebo.”<sup>2660</sup> However, Defendants provide no evidence  
19 that a person or ordinary skill would have had a reasonable expectation of success in a method of  
20 reducing triglycerides in a subject having very-high triglyceride levels by administering purified

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22 <sup>2657</sup> see Section V.O.

23 <sup>2658</sup> see Section III.

24 <sup>2659</sup> Defendants’ Joint Invalidation Contentions at 314.

<sup>2660</sup> Defendants’ Joint Invalidation Contentions at 318.

1 EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore,  
2 Defendants fail to provide a reasonable expectation of success for the claimed invention.

3 Defendants further argue, that “because it was known that DHA and EPA were  
4 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have  
5 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified  
6 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been  
7 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition  
8 with a reasonable expectation of success that such administration would result in reducing  
9 triglycerides while avoiding an increase in LDL.”<sup>2661</sup> Defendants argument is without any basis.  
10 To the contrary, because a person of ordinary skill in the art would have understood DHA and  
11 EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have  
12 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no  
13 explanation and cite to no article to support their argument that the similar effects on TG levels is  
14 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on  
15 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected  
16 *both* EPA and DHA, whether administered alone or in combination, would cause an increase in  
17 LDL-C when administered to the very high TG patient population.

18 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients  
19 with very-high TG. A person of ordinary skill would have thus expected EPA, like  
20 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient  
21 population. It was well known that TG-lowering agents, specifically fibrates and  
22 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but

23 \_\_\_\_\_  
24 <sup>2661</sup> Defendants’ Joint Invalidity Contentions at 322.

1 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art  
2 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the  
3 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including  
4 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as  
5 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2662</sup>	-20%	+45%
Lovaza/Omacor <sup>2663</sup>	-6%	+45%

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10 Accordingly, a person of ordinary skill would not have a reasonable expectation of  
11 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients  
12 with very-high TG levels using EPA.

13 Defendants' position that a person of ordinary skill would have had a reasonable  
14 expectation of success in administering purified EPA to the requisite patient population to  
15 achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that  
16 Defendants' provide no evidence that anyone thought to administer Epadel, which was available  
17 for many years prior to the invention of the '677 patent, to patients with very-high TGs as a  
18 treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified  
19 EPA in the very-high TG population.

20 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
21 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
22

23 <sup>2662</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>2663</sup> Chan 2002 I at 2381 (Table 3).

1 countless studies conducted which administer Epadel and report the effects observed. Although  
2 a few studies administer Epadel to a patient population which included a few patients with TG  
3 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
4 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
5 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
6 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
7 triglycerides.

8 Accordingly, a person of ordinary skill would not have a reasonable expectation of  
9 success in achieving the claimed invention.

10 (2) Dependent Claims

11 (a) Defendants Have Not Shown that Claims 2 and 3 of  
12 the '677 Patent Would Have Been Obvious

13 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
14 Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim  
15 by clear and convincing evidence, they also have not adequately proven the obviousness of  
16 Claims 2 and 3.

17 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach  
18 the additional claim elements of dependent Claims 2 and 3. Defendants contend, without  
19 providing any support, that the claim elements are the results of simply optimizing the conditions  
20 described in the prior art and within the purview of the skilled physicians. These contentions: 1)  
21 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant  
22 to an obvious analysis; 3) fail to address whether the specific combination of claim elements  
23 were all present in the prior art references that would have been combined by a person of  
24 ordinary skill in the art to produce the claimed invention with a reasonable expectation of

1 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
2 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
3 Although convenient and expedient, Defendants’ approach does not conform with the Local  
4 Patent Rules of this District, the law of claim construction, or the law of obviousness.

5 Defendants fail to show a specific combination of references that discloses each element  
6 of the claimed invention. None of the cited references discloses administration of the claimed  
7 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
8 combined to teach the administration of the claimed EPA to very high TG patients.<sup>2664</sup>  
9 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
10 considering other disclosures or even the reference as a whole. Each reference, however, must  
11 be evaluated for all that it teaches.<sup>2665</sup> Defendants’ unsupported cobbling of selective disclosures  
12 represents hindsight reconstruction.<sup>2666</sup>

13 Defendants fail to show a motivation or reason to combine or modify the references  
14 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
15 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not  
16 show why a person of ordinary skill would have been motivated to combine the references to  
17 achieve the claimed invention.<sup>2667</sup>

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19 <sup>2664</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>2665</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>2666</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 <sup>2667</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
23 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
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1 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
2 have successfully achieved the claimed invention. In fact, other than simply identifying prior art  
3 references that purportedly disclose disparate elements, Defendants do not even discuss whether  
4 a person of ordinary skill would have expected that the combination to work for its intended  
5 purpose.<sup>2668</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
6 claimed invention.

7 (b) Defendants Have Not Shown that Claim 4 of the  
8 '677 Patent Would Have Been Obvious

9 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
10 Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim  
11 by clear and convincing evidence, they also have not adequately proven the obviousness of  
12 Claim 4.

13 Defendants contend that it would be obvious that a person receiving the claimed EPA  
14 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50  
15 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean  
16 LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for  
17 the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) fail to  
18 address whether the specific combination of claim elements were all present in the prior art  
19 references that would have been combined by a person of ordinary skill in the art to produce the  
20 claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie*

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in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness  
determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>2668</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
2 point of reading the element out of the claim. Although convenient and expedient, Defendants'  
3 approach does not conform with the Local Patent Rules of this District, the law of claim  
4 construction, or the law of obviousness.

5 Defendants do not identify any combination of references and simply provide a laundry  
6 list of references that purportedly disclose disparate elements without explaining how they can  
7 be combined.<sup>2669</sup> Defendants merely demonstrate that the element was purported known in the  
8 prior art without explaining how it can be combined with other elements.<sup>2670</sup> As such,  
9 Defendants discuss the claim element in isolation, and fail to address the claimed invention as a  
10 whole.<sup>2671</sup> Defendants selectively cite to an unspecified isolated disclosure within a reference  
11 without considering other disclosures or even the reference as a whole. Each reference,  
12 however, must be evaluated for all that it teaches.<sup>2672</sup> Defendants' unsupported cobbling of  
13 selective disclosures represents hindsight reconstruction.<sup>2673</sup>

14 Because Defendants do not identify any combination of references, they necessarily fail  
15 to offer any evidence that a person of skill in the art would be motivated to combine those  
16 references in order to achieve the invention of the claim as a whole. Further, Defendants do not

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18 <sup>2669</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 <sup>2670</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>2671</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

21 <sup>2672</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 <sup>2673</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).



1 discuss at all whether a person of ordinary skill would have been motivated to combine the  
2 elements, other than stating that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or  
3 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment.  
4 Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150  
5 mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs  
6 note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40  
7 mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would  
8 have been motivated to combine the elements to achieve the claimed invention.<sup>2674</sup>

9 Similarly, without the disclosure of a combination of references and a motivation/reason  
10 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
11 person of ordinary skill in the art would have had a reasonable expectation of success in  
12 achieving the claimed invention. In fact, other than simply identifying prior art references that  
13 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
14 ordinary skill would have expected that the combination to work for its intended purpose for  
15 treating the recited patient population.<sup>2675</sup> As such, Defendants fail to demonstrate reasonable  
16 expectation of success of the claimed invention.

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20 <sup>2674</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>2675</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 (c) Defendants Have Not Shown that Claim 5 of the  
2 '677 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
4 Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim  
5 by clear and convincing evidence, they also have not adequately proven the obviousness of  
6 Claim 5.

7 Defendants do not identify any combination of references and simply provide a laundry  
8 list of references without explaining how each reference relates to the claimed invention.  
9 Defendants further contend, without any support, that a person of ordinary skill would have been  
10 able to determine the patient population in need of the claimed methods of treatment, would seek  
11 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat  
12 those patients having very high triglycerides regardless of the baseline values of these lipids.<sup>2676</sup>  
13 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
14 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
15 combination of claim elements were all present in the prior art references that would have been  
16 combined by a person of ordinary skill in the art to produce the claimed invention with a  
17 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
18 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
19 element out of the claim. Although convenient and expedient, Defendants' approach does not  
20 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
21 obviousness.

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<sup>2676</sup> *Id.*

1 Defendants fail to show a specific combination of references that discloses each element  
2 of the claimed invention. Defendants merely list references, without reference to a specific page  
3 or section, that purportedly disclose disparate elements without explaining how they can be  
4 combined.<sup>2677</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
5 the claimed invention as a whole.<sup>2678</sup> Moreover, by simply identifying prior art references  
6 without discussing the specific teachings of each reference, Defendants fail to consider each  
7 prior art reference as a whole.<sup>2679</sup> Each reference must be evaluated for all that it teaches.  
8 Defendants' unsupported cobbling of selective disclosures represents hindsight  
9 reconstruction.<sup>2680</sup>

10 Because Defendants do not identify any combination of references, they necessarily fail  
11 to offer any evidence that a person of skill in the art would be motivated to combine those  
12 references in order to achieve the invention of the claim as a whole. Defendants make a  
13 conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed  
14 methods of treatment, without providing a reason that would have prompted a person of ordinary  
15 skill to combine the elements.<sup>2681</sup> Such a naked assertion does not show why a person of  
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17 <sup>2677</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
18 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art").

19 <sup>2678</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is  
made with respect to the subject matter as a whole, not separate pieces of the claim").

20 <sup>2679</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("A prior  
21 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention  
in suit.") (internal citation and quotation marks omitted).

22 <sup>2680</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention").

23 <sup>2681</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be  
24 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

1 ordinary skill would have been motivated to treat the recited patient population using the claimed  
2 methods of treatment.<sup>2682</sup>

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. In fact, other than simply identifying prior art references that  
7 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
8 ordinary skill would have expected that the combination to work for its intended purpose for  
9 treating the recited patient population.<sup>2683</sup> As such, Defendants fail to demonstrate reasonable  
10 expectation of success of the claimed invention.

11 (d) Defendants Have Not Shown that Claims 6 and 7 of  
12 the '677 Patent Would Have Been Obvious

13 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
14 Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim  
15 by clear and convincing evidence, they also have not adequately proven the obviousness of  
16 Claims 6 and 7.

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underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted)

20 <sup>2682</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR  
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
22 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>2683</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants contend, without support, that the recited reduction in TG represents  
2 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to  
3 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of  
4 ordinary skill to seek to reduce TG by the recited amount because there is no significance  
5 attached to the amount. Defendants conclude, without support, that there was a reasonable  
6 expectation of success without identifying any combination of references and without explaining  
7 how each reference relates to the claimed invention.<sup>2684</sup> These contentions: 1) do not assert  
8 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious  
9 analysis; 3) fail to address whether the specific combination of claim elements were all present in  
10 the prior art references that would have been combined by a person of ordinary skill in the art to  
11 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish  
12 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim  
13 element to the point of reading the element out of the claim. Although convenient and expedient,  
14 Defendants’ approach does not conform with the Local Patent Rules of this District, the law of  
15 claim construction, or the law of obviousness.

16 Defendants further contend, without support, that a person of ordinary skill would  
17 “reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation  
18 containing no DHA,” as a formulation containing both EPA and DHA. Defendants conclude,  
19 without support, that it would have been obvious to administer a composition containing EPA,  
20 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while  
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22 <sup>2684</sup> Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris\_Etherton 2002, Kurabayashi, Leigh-  
23 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney  
24 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,  
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to  
2 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim  
3 elements were all present in the prior art references that would have been combined by a person  
4 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of  
5 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
6 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
7 Although convenient and expedient, Defendants’ approach does not conform with the Local  
8 Patent Rules of this District, the law of claim construction, or the law of obviousness.

9 Defendants do not identify any combination of references and simply provide a laundry  
10 list of references that purportedly disclose disparate elements without explaining how they can  
11 be combined.<sup>2685</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
12 the claimed invention as a whole.<sup>2686</sup> Defendants selectively cite to an unspecified isolated  
13 disclosure within a reference without considering other disclosures or even the reference as a  
14 whole. Each reference, however, must be evaluated for all that it teaches.<sup>2687</sup> Defendants’  
15 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2688</sup>

16 Because Defendants do not identify any combination of references, they necessarily fail  
17 to offer any evidence that a person of skill in the art would be motivated to combine those  
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19 <sup>2685</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*  
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

21 <sup>2686</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is  
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 <sup>2687</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2688</sup> *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 references in order to achieve the invention of the claim as a whole. Defendants make a  
2 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to  
3 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a  
4 person of ordinary skill to reduce triglycerides by the recited amount.<sup>2689</sup> Defendants’ burden to  
5 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”  
6 attached to the recited TG reduction amount.<sup>2690</sup> Defendants have not met the burden with the  
7 naked assertion that it would have been obvious to seek the claim element.

8 Similarly, without the disclosure of a combination of references and a motivation/reason  
9 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
10 person of ordinary skill in the art would have had a reasonable expectation of success in  
11 achieving the claimed invention. Defendants make a conclusory statement that there was a  
12 reasonable expectation of success, without providing a support other than merely identifying  
13 prior art references that purportedly disclose disparate elements.<sup>2691</sup> The mere fact that elements  
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16 <sup>2689</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
17 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
18 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
19 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,  
20 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or  
21 motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason  
22 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the  
23 claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.  
24 398, 418 (2007)).

<sup>2690</sup> Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been  
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*  
case of obviousness by establishing that the claimed range is critical . . . .”) (internal quotation marks omitted).

<sup>2691</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted).

1 are capable of being physically combined does not establish reasonable expectation of  
2 success.<sup>2692</sup>

3 (e) Defendants Have Not Shown that Claim 8 of the  
4 '677 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
6 Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim  
7 by clear and convincing evidence, they also have not adequately proven the obviousness of  
8 Claim 8.

9 Defendants do not identify any combination of references and simply provide a laundry  
10 list of references that purportedly disclose disparate elements without explaining how they can  
11 be combined.<sup>2693</sup> Defendants contend, without providing any support, that it would be obvious  
12 to one of skill in the art to administer a composition containing EPA, but containing no DHA,  
13 with a reasonable expectation of success in reducing Apo-B levels and thus also reduce LDL-C  
14 levels. These contentions: 1) do not assert what the prior art discloses to a person of ordinary  
15 skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
16 combination of claim elements were all present in the prior art references that would have been  
17 combined by a person of ordinary skill in the art to produce the claimed invention with a  
18 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
19 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
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22 <sup>2692</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.”).

23 <sup>2693</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).  
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1 element out of the claim. Although convenient and expedient, Defendants’ approach does not  
2 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
3 obviousness.

4 Defendants fail to show a specific combination of references that discloses each element  
5 of the claimed invention. None of the cited references discloses administration of the claimed  
6 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
7 combined to teach the administration of the claimed EPA to very high TG patients.<sup>2694</sup>  
8 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
9 considering other disclosures or even the reference as a whole. Each reference, however, must  
10 be evaluated for all that it teaches.<sup>2695</sup> Defendants’ unsupported cobbling of selective disclosures  
11 represents hindsight reconstruction.<sup>2696</sup>

12 Defendants fail to show a motivation or reason to combine or modify the references  
13 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
14 would have been obvious but such a naked assertion does not show why a person of ordinary  
15 skill would have been motivated to combine the references to achieve the claimed invention.<sup>2697</sup>

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18 <sup>2694</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 <sup>2695</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 <sup>2696</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 <sup>2697</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
23 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
2 have successfully achieved the claimed invention. In fact, Defendants do not even discuss  
3 whether a person of ordinary skill would have expected that the combination to work for its  
4 intended purpose.<sup>2698</sup> As such, Defendants fail to demonstrate reasonable expectation of success  
5 of the claimed invention.

6 Beyond their laundry list of citations, Defendants rely on only one reference in their  
7 invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the  
8 asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that “it was  
9 known that Apo-B is a component of LDL-C.” Defendants cite to no passage or page of  
10 Theobald in connection with that argument and no support for their argument that Theobald  
11 makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C  
12 but ignore that Apo-B is present on all atherogenic lipoproteins.<sup>2699</sup>

13 Defendants then make the unsupported assertion that “one of ordinary skill in the art  
14 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to  
15 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald  
16 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render  
17 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis  
18 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL  
19 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with  
20 respect to this claim or Apo-B levels.

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22 <sup>2698</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

24 <sup>2699</sup> June 26, 2012 Bays Declaration; *see also* Section III.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a component of LDL-C, they fail to discuss the reference's disclosures regarding the impact of administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference.<sup>2700</sup>

TABLE 3  
Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect <sup>1</sup>
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 <sup>2</sup>	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) <sup>3</sup>
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) <sup>4</sup>
HDL cholesterol (mmol/L) <sup>5</sup>	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) <sup>6</sup>	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
<b>Apolipoprotein B (g/L)</b>	<b>0.84 ± 0.027</b>	<b>0.87 ± 0.026</b>	<b>0.83 ± 0.028</b>	<b>0.84 ± 0.028</b>	<b>0.03 (0.002, 0.055)<sup>7</sup></b>
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) <sup>3</sup>
Weight (kg) <sup>8</sup>	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

<sup>1</sup> Mean difference between active treatment and placebo; 95% CI in parentheses.

<sup>2</sup>  $\bar{x} \pm \text{SEM}$  (all such values);  $n = 38$ .

<sup>3,4,7</sup> Paired  $t$  test: <sup>3</sup> $P = 0.04$ , <sup>4</sup> $P = 0.004$ , <sup>7</sup> $P = 0.03$ .

<sup>5</sup> HDL increased in subjects receiving DHA first. Significant treatment  $\times$  order effect,  $P = 0.005$ .

<sup>6</sup>  $n = 37$ ; data were log transformed before analysis by paired  $t$  test.

<sup>8</sup> Weight increased over the entire study period. Significant order  $\times$  time effect,  $P = 0.001$ .

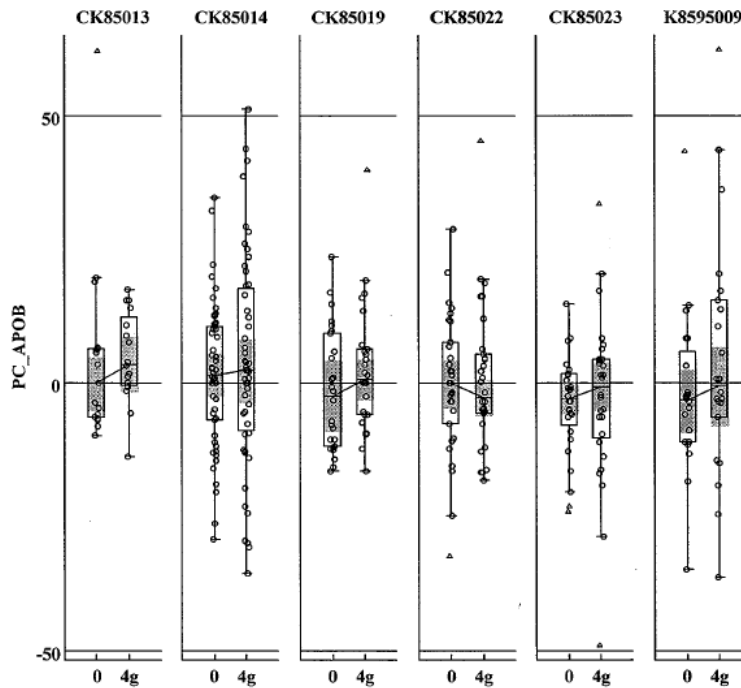
As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases Apo-B levels in very high TG patients.

A person of skill in the art would *not* have understood that EPA therapy in very high TG patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on

<sup>2700</sup> Theobald at 561, table 3.

1 Apo-B levels in patients with very high TG levels.<sup>2701</sup> The Lovaza clinical trial, which was a  
2 large study conducted on patients with very high TG levels, shows no difference between a  
3 placebo-control group and the treatment group with respect to Apo-B levels.<sup>2702</sup>

14. Box plot of individual Category I studies -% change of APOB



16 In each of these studies, including K8595009, where subjects had a median baseline TG  
17 level of 818 mg/dL,<sup>2703</sup> there was no change in Apo-B between the control and treatment groups.  
18 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected  
19 that treatment with Lovaza did not impact Apo-B compared to placebo.<sup>2704</sup>

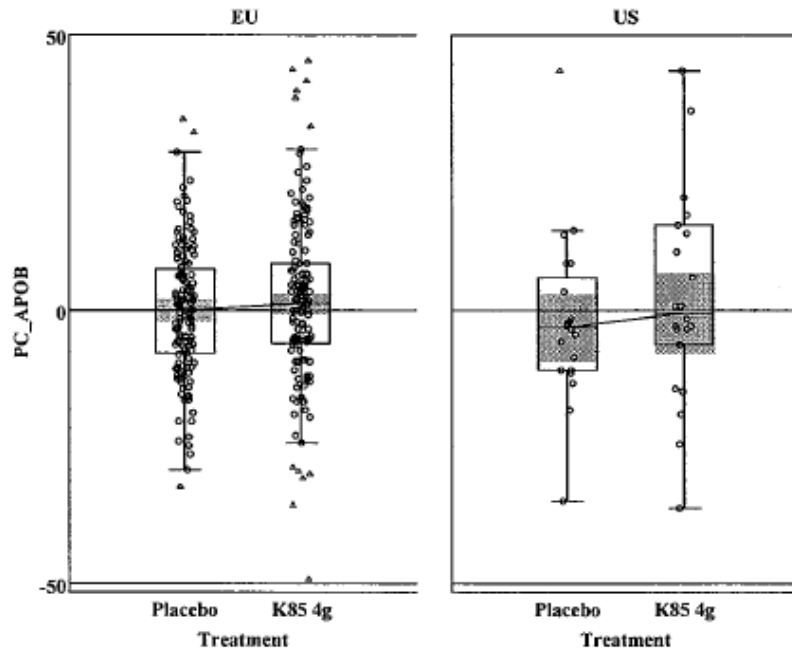
22 <sup>2701</sup> May 8, 2012 Bays Declaration.

23 <sup>2702</sup> Lovaza Approval Package at Table 14.

24 <sup>2703</sup> The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

<sup>2704</sup> Lovaza Approval Package at Table 7.

7. Box plot of pooled Category I studies -% change of APOB



Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.<sup>2705</sup> While Theobald does not even support Defendants' obviousness arguments, their selective citation of that reference represents impermissible hindsight bias. The examiner had before him a large number of prior art references reporting Apo-B effects and, even as defendants concede, agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of

<sup>2705</sup> See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of  
2 success.<sup>2706</sup>

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the  
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.<sup>2707</sup> The person of  
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels  
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As  
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic  
8 lipoproteins, but instead smaller, denser particles referred to as remnant.<sup>2708</sup> Accordingly,  
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because  
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of  
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients  
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to  
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art  
15 have been motivated to administer the EPA composition of the claimed invention to very high  
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a  
17 reasonable expectation of success in achieving the claimed invention.

18  
19 (f) Defendants Have Not Shown that Claim 9 of the  
'677 Patent Would Have Been Obvious

20 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
21 Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim

22 \_\_\_\_\_  
<sup>2706</sup> Defendants' Contentions at 236.

23 <sup>2707</sup> ATP-III at 3170; Bays 2008 I at 395.

24 <sup>2708</sup> Kwiterovich in Kwiterovich at 4.

1 by clear and convincing evidence, they also have not adequately proven the obviousness of  
2 Claim 9.

3 Defendants contend that it would have been obvious to use the claimed composition to  
4 reduce VLDL-C levels, and that the claimed VLDL-C reduction represents therapeutic efficacy,  
5 citing a laundry list of references without explaining how each reference relates to the claimed  
6 invention.<sup>2709</sup> These contentions: 1) do not assert what the prior art discloses to a person of  
7 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the  
8 specific combination of claim elements were all present in the prior art references that would  
9 have been combined by a person of ordinary skill in the art to produce the claimed invention  
10 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.

11 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of  
12 reading the element out of the claim. Although convenient and expedient, Defendants' approach  
13 does not conform with the Local Patent Rules of this District, the law of claim construction, or  
14 the law of obviousness.

15 Defendants do not identify any combination of references and simply provide a laundry  
16 list of references that purportedly disclose disparate elements without explaining how they can  
17 be combined.<sup>2710</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
18 the claimed invention as a whole.<sup>2711</sup> Defendants selectively cite to an unspecified isolated  
19 disclosure within a reference without considering other disclosures or even the reference as a

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20 <sup>2709</sup> *Id.*

21 <sup>2710</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

23 <sup>2711</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is  
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 whole. Each reference, however, must be evaluated for all that it teaches.<sup>2712</sup> Defendants’  
2 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2713</sup>

3 Because Defendants do not identify any combination of references, they necessarily fail  
4 to offer any evidence that a person of skill in the art would be motivated to combine those  
5 references in order to achieve the invention of the claim as a whole. In fact, Defendants do not  
6 discuss at all whether a person of ordinary skill would have been motivated to combine the  
7 elements.<sup>2714</sup> As such, Defendants fail to demonstrate that there was no motivation to combine  
8 the references to achieve the claimed invention.

9 Similarly, without the disclosure of a combination of references and a motivation/reason  
10 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
11 person of ordinary skill in the art would have had a reasonable expectation of success in  
12 achieving the claimed invention. Defendants make a conclusory statement that a person of  
13 ordinary skill would naturally seek to reduce VLDL-C levels to a therapeutic level, without  
14 providing a support other than simply identifying prior art references that purportedly disclose  
15 disparate elements.<sup>2715</sup> The mere fact that elements are capable of being physically combined  
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17 <sup>2712</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

18 <sup>2713</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
19 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
20 without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 <sup>2714</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
23 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

<sup>2715</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted).



1 does not establish reasonable expectation of success.<sup>2716</sup> What is more, Defendants do not even  
2 discuss the reasonable expectation of reducing VLDL-C levels. As such, Defendants fail to  
3 demonstrate reasonable expectation of success of reducing VLDL-C levels using the claimed  
4 methods.

5 **4. The ‘677 Patent is Not Invalid Under § 112**

6 a) Defendants Have Not Demonstrated that the Claims of the ‘677  
7 Patent Are Invalid for Indefiniteness

8 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]  
9 the subject matter which the applicant regards as his invention.”<sup>2717</sup> Patent claims are valid in  
10 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the  
11 art about the scope of the invention” in light of the specification and the prosecution history.<sup>2718</sup>  
12 The Supreme Court has recognized that “absolute precision is unattainable” in claim language  
13 and “the certainty which the law requires in patents is not greater than is reasonable.”<sup>2719</sup>

14 Defendants allege that a number of terms containing the phrases “about” and  
15 “substantially” are indefinite. Defendants do not provide any reason why these terms are  
16 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,  
17

18 \_\_\_\_\_  
19 <sup>2716</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
20 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
21 combined, but also that the combination would have worked for its intended purpose.”).

22 <sup>2717</sup> Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and  
23 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite  
24 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions  
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from  
supplementing their naked assertions with new basis in the course of the litigation.

<sup>2718</sup> *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

<sup>2719</sup> *Id.* at 2129.

1 these terms are routinely used in patent claims, and are not *per se* indefinite.<sup>2720</sup> In particular,  
2 courts have held repeatedly that claims that contain the words “about” and “substantially” are not  
3 indefinite.<sup>2721</sup> Here, a person of ordinary skill would understand with reasonable certainty what  
4 is claimed when the claims are read in light of the specification and prosecution history.<sup>2722</sup>  
5 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being  
6 indefinite.

7 Defendants further allege that the terms “4g per day of a pharmaceutical composition  
8 comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” are  
9 indefinite. They contend that, because there is no indication of how much of the pharmaceutical  
10 composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid  
11 is present in the composition. This is incorrect. A claim can use a ratio to define amounts of  
12 components in a product, using terms such as “percent by weight.”<sup>2723</sup> In light of the  
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14 <sup>2720</sup> *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms  
15 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the  
16 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.  
17 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the  
18 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d  
19 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe  
20 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish  
21 the claimed subject matter from the prior art, it is not indefinite.”).

18 <sup>2721</sup> *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim  
19 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.  
20 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction  
21 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy  
22 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration  
23 as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,  
24 1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not  
indefinite).

22 <sup>2722</sup> *See generally* the ’677 patent and its prosecution history.

23 <sup>2723</sup> *T.F.H. Publications, Inc. v. Daskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at \*5–6 (D.N.J.  
24 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a  
second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at \*10 (E.D. Tex. Apr. 27,

1 specification and prosecution history, a person of ordinary skill would understand with  
2 reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the  
3 recited pharmaceutical composition in relation to all fatty acids present.<sup>2724</sup> Therefore, these  
4 terms are not indefinite and do not render the claims indefinite.

5 Defendants also allege that it is impossible to ascertain the metes and bounds of  
6 “compared to placebo control.” A person of ordinary skill, however, would understand the  
7 metes and bounds of the term in light of the specification and the prosecution history.<sup>2725</sup>  
8 Moreover, the method of comparing a subject to a placebo control, such as a placebo controlled,  
9 randomized, double blind study, would have been known to a person of ordinary skill at the time  
10 of the invention. Therefore, the term does not render the claims indefinite.

11 Finally, Defendants contend that the asserted claims improperly mix methods and  
12 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that  
13 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness  
14 analysis is based on what the claim language informs a person of ordinary skill in the art in light  
15 of the specification and the prosecution history. Defendants do not identify any actual claim  
16 language that mixes methods and formulations. Moreover, contributory infringement may be  
17 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*  
18 *process . . . knowing the same to be especially made or especially adapted for use in an*  
19 *infringement of such patent.*”<sup>2726</sup> Plaintiffs assert that Defendants’ ANDA products will be used

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21 2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total  
22 volume of the solution, with this ratio expressed as a percentage”).

23 <sup>2724</sup> See generally the ’677 patent and its prosecution history.

24 <sup>2725</sup> See generally the ’677 patent and its prosecution history.

<sup>2726</sup> 35 U.S.C. § 271(c) (emphasis added).

1 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound  
2 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are  
3 mistaken and the ’677 patent claims are not indefinite for improperly mixing methods and  
4 formulations.

5 b) Defendants Have Not Demonstrated that the Claims of the ’677  
6 Patent Are Invalid for Insufficient Written Description

7 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a  
8 written description of the invention.” This requires that the specification “reasonably convey” to  
9 a skilled artisan that the applicant “invented” or “had possession” of the claimed subject matter  
10 when the application was filed.<sup>2727</sup> Support need not be literal<sup>2728</sup>—it may be implicit<sup>2729</sup> or  
11 inherent<sup>2730</sup> in the disclosure. In addition, it is unnecessary to include information that is already  
12 known or available to persons of ordinary skill.<sup>2731</sup>

13 Defendants make three arguments regarding the written description requirement. First,  
14 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack  
15 written description. This is incorrect. The specification of asserted patents literally discloses the  
16 claimed invention.<sup>2732</sup> Moreover, the recited baseline TG levels of the claimed invention appear

17 <sup>2727</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

18 <sup>2728</sup> *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d  
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

19 <sup>2729</sup> *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866  
F.2d at 424–25.

20 <sup>2730</sup> *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

21 <sup>2731</sup> *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,  
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

22 <sup>2732</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
23 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
24 legal foundation for claiming that species.”).

1 in the original claims of the application to which the asserted patent claims priority. Thus, there  
2 is a strong presumption that the claimed invention is adequately described.<sup>2733</sup> Defendants do  
3 not and cannot rebut this presumption. Specifically, the patient population is originally claimed  
4 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500  
5 mg/dl.”<sup>2734</sup> The asserted claims recite the same patient population. Defendants do not contend  
6 that the patient population of the asserted claims is not literally described by the specification  
7 and in the original claims of the application to which the asserted patent claims priority. In fact,  
8 the specification and the provisional patent application claims at the time of filing describe these  
9 limitations.<sup>2735</sup> Therefore, Defendants have failed to explain whether and how an aspect of the  
10 claimed invention has not been described with sufficient particularity such that one skilled in the  
11 art would recognize that the applicant had possession of the claimed invention.

12                 Second, Defendants contend that “a person of skill in the art would not understand  
13 that the inventor was in possession of a method incorporating [] specific dosages and quantities.”  
14 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the  
15 dosages and quantities of the claimed methods.<sup>2736</sup> Moreover, the dosages and quantities of the  
16 method appear in the claims, as originally filed. Thus, there is a strong presumption that the  
17  
18

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19 <sup>2733</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
20 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

21 <sup>2734</sup> See U.S. Application No. 12/702,889.

22 <sup>2735</sup> ‘677 patent at 13:29-34; 14:29-51; U.S. Provisional Application No. 61/151,291.

23 <sup>2736</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
24 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
legal foundation for claiming that species.”).

1 | claimed invention is adequately described.<sup>2737</sup> Defendants do not and cannot rebut this  
2 | presumption. For example, the dosage of the composition was originally claimed as “about 1 g  
3 | to about 4g.”<sup>2738</sup> The asserted claims recite “4 g.” Defendants do not contend that dosages and  
4 | quantities of the asserted claims are not literally described by the specification and in the original  
5 | claims. In fact, the specification and the provisional patent application claims, at the time of  
6 | filing, described these limitations. Therefore, Defendants have failed to explain whether and  
7 | how an aspect of the claimed invention has not been described with sufficient particularity such  
8 | that one skilled in the art would recognize that the applicant had possession of the claimed  
9 | invention.

10 |       Third, Defendants appear to suggest, although they have not specifically contended, that  
11 | “a person of skill in the art would not understand that the inventor was in possession of a method  
12 | comprising a comparison against” placebo control. The specification demonstrates that the  
13 | applicants were in possession of the claimed inventions. For example, a person of ordinary skill  
14 | would have understood that the inventor was in possession of a method comprising  
15 | administration of a composition with the recited properties, based on a comparison of a subject  
16 | or a population against placebo control.

17 |       In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,<sup>2739</sup>  
18 | the court elaborated that “possession” means possession as evidenced by disclosure. In this case,  
19 | the specification of asserted patents literally disclose the claimed invention in the specification  
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22 | <sup>2737</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

23 | <sup>2738</sup> See U.S. Provisional Application No. 61/151,291.

24 | <sup>2739</sup> *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

1 and the claims as originally filed. Thus, an examination of the four corners of the specification  
2 from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the  
3 asserted patents were in possession of the claimed invention.

4 Defendants conclude by alleging that the specification does not describe anything more  
5 than what is obvious, and thus does not provide adequate support for any nonobvious claim.  
6 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the  
7 specification; nonobviousness can be supported by post-filing date evidence for example.<sup>2740</sup>  
8 Written description requires only that the specification reasonably conveys that the applicant had  
9 possession of the claimed subject matter when the application was filed. Therefore, whether the  
10 claims are obvious has no bearing on the adequacy of written description.

11 c) Defendants Have Not Demonstrated that the Claims of the '677  
12 Patent Are Invalid for Lack of Enablement

13 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person  
14 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would  
15 require undue experimentation for a person of ordinary skill to make or use the invention.  
16 Factors that may be considered include the quantity of experimentation necessary, the amount of  
17 direction or guidance presented, the presence or absence of working examples, the nature of the  
18 invention, the state of the prior art, the relative skill of those in the art, the predictability or  
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20 <sup>2740</sup> See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)  
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is  
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those  
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,  
24 1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained  
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.  
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full  
range of an invention is not always achieved at the time of filing the patent application.”).

1 unpredictability of the art, and the breadth of the claims.<sup>2741</sup> The enablement requirement is  
2 separate and distinct from the written description requirement,<sup>2742</sup> and as such a claim does not  
3 require descriptive support in the disclosure as originally filed for it to be enabled.<sup>2743</sup>

4 Defendants make two specific arguments regarding the enablement requirement. First,  
5 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of  
6 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the  
7 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary  
8 skill would be able to determine the amounts of the components in the pharmaceutical  
9 composition without any experimentation, much less undue experimentation.

10 Second, Defendants contend that it would take undue experimentation to obtain the  
11 claimed required results listed in the full scope of the patent claims, including the claimed lipid  
12 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed  
13 method and certainly not undue experimentation. Administration of a recited amount of a recited  
14 composition, for a recited duration, to a specific, recited patient population produces the recited  
15 results. No additional experimentation is required, and Defendants do not explain their  
16 allegation that undue experimentation would be required. Defendants also do not contend that  
17 following the claimed method (each recited element) does not produce the recited results. The  
18 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly  
19 demonstrate that administration of EPA of the recited composition, when administered to  
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22 <sup>2741</sup> See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 <sup>2742</sup> *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 <sup>2743</sup> MPEP § 2164.



1 patients with very high TG levels for at least 12 weeks, as specified, produces the recited  
2 results.<sup>2744</sup> Therefore, the claims are not invalid for lack of enablement.

3 Defendants conclude by alleging that the specification does not enable anything more  
4 than what is obvious over the prior art or was known to a person of skill in the art. First,  
5 Defendants do not cite any case or present a legal theory to support this assertion. As such, they  
6 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be  
7 precluded in the future from raising any new legal theory to support this assertion. Moreover,  
8 while the '677 patent's specification enables a person of ordinary skill to obtain the claimed  
9 limitations without undue experiment, the claimed limitations would not have been obvious to a  
10 person of ordinary skill, as discussed in Section V.E.3. Furthermore, Plaintiffs have initiated  
11 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its  
12 claimed methods.<sup>2745, 2746</sup> Therefore, a person of ordinary skill would have concluded that the  
13 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

14 **F. The '446 Patent**

15 **1. The '446 Patent Claims Eligible Subject Matter Under § 101**

16 Defendants' allegation that the asserted claims of the '446 patent relate to ineligible  
17 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*  
18 case under Section 101 or provide a legal or factual basis to support their allegations.

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21 <sup>2744</sup> See VASCEPA Prescribing Information at Table 2.

22 <sup>2745</sup> *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any  
23 doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical  
24 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that  
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.").

<sup>2746</sup> See May 16, 2011 Bays Declaration at Appendix B.

1 As an initial matter, Defendants’ disclosure is also insufficient under the Nevada Local  
2 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be  
3 provided.<sup>2747</sup> The bare assertion of invalidity under Section 101 without providing the grounds  
4 for such an allegation and examining the elements of the asserted claims of the ’446 patent does  
5 not meet this requirement and thwarts the purpose of the Rules.<sup>2748</sup>

6 The inquiry under Section 101 involves a two-step test: first, a court must determine  
7 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical  
8 phenomenon, or abstract idea.<sup>2749</sup> Second, even if the claim is directed to one of these concepts,  
9 it still may be patent eligible and the court must determine what else is part of the claim.<sup>2750</sup>

10 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*  
11 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of  
12 the ’446 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]  
13 conventional” steps, and the only novel element related to administering the proper dosage based  
14 on a natural law observation.<sup>2751</sup> However, the claims merely recited this natural law without  
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16 <sup>2747</sup> See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all  
17 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed  
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

18 <sup>2748</sup> Nor does the preceding paragraph, which provides only a purported summary of the claims of the ’446 patent, or  
19 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the  
20 grounds for Defendants’ allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,*  
*Inc. v. Garmin Int’l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent  
21 Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide  
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those  
22 contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

23 <sup>2749</sup> *Alice Corp. Pty. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at  
24 issue are directed to one of those patent-ineligible concepts.”).

<sup>2750</sup> *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

<sup>2751</sup> *Mayo*, 132 S. Ct. at 1294.

1 reciting any novel application of it.<sup>2752</sup> The Court found that providing protection to such  
2 claims would result in pre-empting “a broad range of potential uses” and excluding others from  
3 using “the basic tools of scientific and technical work.”<sup>2753</sup> A method of treatment claim,  
4 specifying the subjects, dosage levels, composition, and time course does not raise the concerns  
5 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent  
6 protection.<sup>2754</sup>

7 Defendants suggest that the recited EPA composition of each asserted claim is a naturally  
8 occurring substance. It is not. Even references contained within Defendants’ own contentions  
9 make clear that EPA of the requisite purity and characteristics is not found in nature.<sup>2755</sup> As  
10 expressed by the patents cited in Defendants’ contentions and well-established precedent, for  
11 decades it has been accepted that compositions isolated from nature or purified beyond their  
12 natural state are patent-eligible.<sup>2756</sup> Moreover, Defendants’ assertions are immaterial to a Section  
13 101 defense because method of treatment claims like the ones asserted in this case are patent  
14 eligible even if they are directed to administration of a naturally occurring substance.<sup>2757</sup>

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16 <sup>2752</sup> *Id.* at 1301.

17 <sup>2753</sup> *Id.*

18 <sup>2754</sup> *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way  
19 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability  
20 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula  
and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d  
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent  
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

21 <sup>2755</sup> *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative  
22 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

23 <sup>2756</sup> *See, e.g., In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394  
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

24 <sup>2757</sup> *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

1 To the extent Defendants are arguing that a law of nature both underlies the claims and  
2 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the  
3 claimed effects are the natural result of ingesting a naturally-occurring substance.”<sup>2758</sup> Since the  
4 composition that is the subject of the claims is not naturally occurring, Defendants appear to  
5 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states  
6 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad  
7 characterization of laws of nature.<sup>2759</sup> To say that the claims of the ’446 patent claim a law of  
8 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode  
9 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to  
10 underlying principles of nature” that would “make all inventions unpatentable.”<sup>2760</sup> Indeed, even  
11 those concerned about the implications of *Mayo* on future patents were focused on diagnostic  
12 claims not treatment claims of the type that *Mayo* stated were typical and patentable.<sup>2761</sup>

13 Even if there is some underlying law of nature in the asserted claims, the subject matter  
14 of the ’446 patent remains eligible for protection under Section 101. As articulated by *Mayo* and  
15 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to  
16 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to  
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18 <sup>2758</sup> See Defendants’ Joint Invalidation Contentions at 429.

19 <sup>2759</sup> See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes  
20 to achieve a desired outcome . . . . That one way of describing the process is to describe the natural ability of the  
21 subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we  
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability  
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to  
aspirin).”).

22 <sup>2760</sup> See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

23 <sup>2761</sup> See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying  
24 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,  
particularly in the area of diagnostic research.”).

1 foreclose from others the use of that equation in conjunction with all of the other steps in their  
2 claimed process.”<sup>2762</sup> As discussed above, the asserted claims of the ’446 patent contain a  
3 novel, unconventional, and specific method of treatment comprising a particularized application  
4 of a nonnaturally occurring substance and does not preempt the use of a law of nature.<sup>2763</sup>

5 Defendants also argue that any argument by Amarin in response to Defendants’ § 112  
6 arguments are further evidence of invalidity under § 101. This argument is without merit. The  
7 claims are enabled and written description is satisfied for the reasons discussed below. In  
8 addition, as discussed above, the asserted claims are not merely a naturally-occurring  
9 phenomena, and thus satisfy the requirements of § 101.

## 10 2. The Asserted Claims of the ‘446 Patent Are Not Anticipated by WO 11 ‘118

12 To anticipate, a single prior art reference must sufficiently describe a claimed  
13 invention so that the public is in “possession” of that invention.<sup>2764</sup> Therefore, to anticipate, a  
14 reference must set forth every element of the claim, either expressly or inherently, in as complete  
15 detail as is contained in the claim.<sup>2765</sup> The claim elements must also be “arranged” in the prior  
16 art reference, just as they are in the claim,<sup>2766</sup> rather than as “multiple, distinct teachings that the  
17 artisan might somehow combine to achieve the claimed invention.”<sup>2767</sup> In addition, public

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18 <sup>2762</sup> See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

19 <sup>2763</sup> See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at \*4 (C.D. Cal. July 24, 2012)  
(rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was  
20 “just one step in the whole process” claimed by the invention).

21 <sup>2764</sup> *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

22 <sup>2765</sup> *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.  
23 Cir. 1989).

24 <sup>2766</sup> *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

<sup>2767</sup> *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587  
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

1 “possession” requires that the prior art enable a person of ordinary skill to make and use the  
2 invention without undue experimentation.<sup>2768</sup> Factors that may be included in this analysis  
3 include the quantity of experimentation necessary, the amount of direction or guidance  
4 presented, the presence or absence of working examples, the nature of the invention, the state of  
5 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,  
6 and the breadth of the claims.<sup>2769</sup> This inquiry is objective, and thus evidence of undue  
7 experimentation need not be prior art.<sup>2770</sup>

8 Defendants assert that Claims 1-11 of the '446 Patent are anticipated by the WO '118  
9 reference.<sup>2771</sup>

10 A element-by-element analysis, identifying each element of each asserted claim that is  
11 absent from WO '118, is provided below. The contentions below are incorporated by reference  
12 into Exhibit F, and vice-versa. WO '118 does not anticipate the claims of the '446 patent  
13 because it does not describe, properly arrange, or enable the '446 patent claims.

14 a) WO '118 Does Not Teach Every Element of the Claims of the  
15 '446 Patent

16 (1) WO '118 Does Not Describe the Claimed Lipid Effects

17 It is well established that, for a prior art reference to anticipate, “every element of the  
18

19 <sup>2768</sup> *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

20 <sup>2769</sup> *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

21 <sup>2770</sup> *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999  
22 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.  
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822  
F.2d 1074, 1078 (Fed. Cir. 1987).

23 <sup>2771</sup> References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs  
24 reserve their right to obtain a certified translation of WO '118.

1 | claimed invention must be identically shown in a single reference.”<sup>2772</sup> Moreover, the elements  
2 | of the claimed invention must have “strict identity” with the elements of the reference; “minimal  
3 | and obvious” differences are sufficient to prevent anticipation.<sup>2773</sup> Here, WO ‘118 entirely fails  
4 | to disclose the following elements of Claim 1 of the ‘446 Patent: *to effect a reduction in*  
5 | *triglycerides without substantially increasing LDL-C compared to placebo control.* Defendants  
6 | appear to concede that WO ‘118 does not expressly teach these elements, as they fail to set forth  
7 | any basis for concluding that WO ‘118 teaches this element.<sup>2774</sup> Indeed, Defendants could not  
8 | set forth any basis for concluding that WO ‘118 teaches this element because WO ‘118 does not.

9 |         Instead, Defendants argue that these elements express the intended result of a method that  
10 | is positively recited, and therefore is inherently anticipated. However, for the reasons set forth  
11 | below, WO ‘118 fails to disclose each element of the independent claim of the ‘446 Patent, either  
12 | expressly or inherently. Therefore, WO ‘118 cannot anticipate the claimed method. Defendants  
13 | also argue that these elements represent inherent, natural properties of EPA, and are entitled to  
14 | no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation  
15 | and claim construction. Further, while Defendants argue that the inherent properties are  
16 | exemplified in the prior art, they fail to identify even a single prior art reference that makes such  
17 | a disclosure. Defendants cannot point to a single, specific prior art reference because the  
18 | claimed pharmaceutical composition has never been administered in the manner claimed to the  
19 | claimed patient population. Also, these elements are positively recited in the body of the claim  
20 | and therefore cannot be construed as a non-limiting preamble and must be given patentable

21 | \_\_\_\_\_  
22 | <sup>2772</sup> *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*  
*Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

23 | <sup>2773</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 | <sup>2774</sup> Defendants’ Invalidation Contentions at 202-204.

1 weight.

2 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid  
3 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
4 inherently anticipate as a matter of law.”<sup>2775</sup> “[A]nticipation by inherent disclosure is appropriate  
5 only when the reference discloses prior art that must *necessarily* include the unstated  
6 limitation.”<sup>2776</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
7 possibly present’ in the prior art.”<sup>2777</sup> WO ‘118 fails to provide any data related to the lipid  
8 effects of the disclosed invention on patients described in the publication. Therefore, Defendants  
9 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets  
10 the elements of the independent claim every time it is administered.

11 Defendants fail to demonstrate that administration of the claimed EPA compositions  
12 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants  
13 suggests that EPA administration may increase LDL-C.<sup>2778</sup> Rambjor is a clinical study which  
14 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA  
15 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a  
16 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*  
17 decrease TG without increasing LDL-C *every time it is administered*.

18 Therefore, WO ‘118 cannot anticipate the independent claim of the ‘446 patent. Because  
19 the dependent claims include all of the claim elements of the independent claim, WO’ 118  
20 cannot anticipate any of the dependent claims as well.

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22 <sup>2775</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>2776</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 <sup>2777</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

<sup>2778</sup> *See, e.g., Rambjor*.



1 (2) WO '118 Does Not Disclose Methods of Treating The  
2 Claimed Patient Population

3 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition  
4 be administered in the manner claimed to the claimed patient population. Defendants attempt to  
5 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is  
6 the introductory clause of a patent claim and includes everything from the beginning of the claim  
7 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the  
8 preamble.

9 A claim preamble has patentable weight if, “when read in the context of the entire claim,  
10 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,  
11 and vitality’ to the claim.”<sup>2779</sup> Additionally, the preamble constitutes a claim element when the  
12 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and  
13 claim body to define the claimed limitation.”<sup>2780</sup>

14 The preamble of the asserted claims is limiting for several reasons. The term “subject” in  
15 the preamble of the independent claim defines and provides antecedent basis for the “subject”  
16 recited in the body of the claims. When reading the claim, one must rely on both the preamble  
17 and the claim body to define the claimed invention.

18 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is  
19 properly construed as a limitation of the claim itself.”<sup>2781</sup> The recitation of a “method of

20 \_\_\_\_\_  
21 <sup>2779</sup> *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

22 <sup>2780</sup> *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

23 <sup>2781</sup> *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer*  
24 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases  
“portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a  
necessary and defining aspect of the invention, specifically its portability,” and because the specification and  
prosecution history “emphasize this feature of the invention”).

1 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing  
2 triglycerides in the body of the claim and emphasizes the intentional purpose for which the  
3 method must be performed - to reduce triglycerides.

4 It is clear that “the claim drafter chose to use both the preamble and the body of the claim  
5 to define the subject matter of the claimed invention.”<sup>2782</sup> Thus, the entire preamble in the  
6 independent claim of the ‘446 must contain patentable weight.

7 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.  
8 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be  
9 administered in the manner claimed to the claimed patient population.

10 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,  
11 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**  
12 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the  
13 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence  
14 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and  
15 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden  
16 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest  
17 angina and exercise-induced angina, and destabilization of the angina.”<sup>2783</sup> The invention of WO  
18 ‘118 is intended to be administered to any person in need of prevention of the occurrence of  
19 cardiovascular events, who are typically hypercholesterolemia patients.<sup>2784</sup> WO ‘118 does not  
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<sup>2782</sup> *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

23 <sup>2783</sup> WO ‘118 at 12.

24 <sup>2784</sup> *Id.*

1 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot  
2 anticipate the independent claim.

3 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail  
4 to prove that these elements of the claimed invention have “strict identity” with the elements of  
5 the reference.<sup>2785</sup> WO ‘118 fails to anticipate this claim element because the broad disclosure  
6 fails to anticipate the narrow claimed range, and the specific patient population defined in the  
7 claims is an essential part of the claimed invention.

8 There is no evidence in that subject as described in the claims were ever treated. In fact,  
9 WO ‘118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the  
10 definition of “hypertriglyceridemia” in WO ‘118 to argue that WO ‘118 discloses treatment of  
11 the subject as described in the claims. It does not. Defendants’ argument rests on the definition  
12 in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150  
13 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working  
14 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels  
15 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any  
16 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as  
17 evidence that a “person of ordinary skill in the art would have understood that the term  
18 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of  
19 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable  
20 and then merely provides examples of commercially available “soft capsules,” such as Omacor.  
21 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients  
22 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be

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24 <sup>2785</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’  
2 or ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”<sup>2786</sup> Therefore,  
3 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO  
4 ‘118 meets the claim elements of the independent claim every time it is administered.

5 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges  
6 claimed by the ‘446 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500  
7 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between  
8 330 and 450 degrees. The court found that the broader prior art range could not anticipate the  
9 claimed temperature range, “[g]iven the considerable difference between the claimed range and  
10 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the  
11 claimed range with sufficient specificity to anticipate this element of the claim.”<sup>2787</sup> A prior art’s  
12 teaching of a broad genus does not necessarily disclose every species within that genus. The  
13 court explained the slightly overlapping range between the preferred range and claimed range “is  
14 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>2788</sup> and therefore  
15 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of  
16 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not  
17 anticipate the subject as described in the claims because it fails to described the claimed TG  
18 range with sufficient specificity.

19 The court in *Atofina* ruled on an additional question of anticipation that also involved a  
20 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

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22 <sup>2786</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>2787</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

24 <sup>2788</sup> *Atofina*, 441 F.3d at 1000.

1 compared to the patent’s claimed range of 0.1 to 5.0 percent.<sup>2789</sup> The court explained that  
2 “although there is a slight overlap, no reasonable fact finder could determine that this overlap  
3 describes the entire claimed range with sufficient specificity to anticipate this limitation of the  
4 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”<sup>2790</sup> Similarly,  
5 although there may be overlap between the definition of hypertriglyceridemia taught by WO  
6 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not  
7 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500  
8 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of  
9 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels  
10 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic  
11 events as the primary clinical objective),<sup>2791</sup> WO ‘118, therefore, does not expressly disclose the  
12 specific patient population that is an essential element of the claims of the asserted patents.  
13 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

14 The treatment of a patient with elevated TG levels varies depending on their serum  
15 triglyceride levels. Identification of the patient population with very high TG levels (at least 500  
16 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,  
17 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment  
18 of lipid disorders.<sup>2792</sup> The ATP-III divided hypertriglyceridemia patients into three classes based  
19 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),  
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21 <sup>2789</sup> *Id.*

22 <sup>2790</sup> *Id.*

23 <sup>2791</sup> *See* Section III.

24 <sup>2792</sup> *Id.*

1 and very-high TGs ( $\geq 500$  mg/dL)—and recommended substantially different treatment  
2 strategies for patients depending on classification.<sup>2793</sup> For the borderline-high and high TG  
3 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.<sup>2794</sup>  
4 Accordingly, in these populations, physicians focused on lowering LDL-C.<sup>2795</sup> In this patient  
5 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.  
6 In contrast, the primary goal for very-high TG patients ( $\geq 500$  mg/dL) was to reduce the risk of  
7 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated  
8 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary  
9 treatment goal.<sup>2796</sup> Therefore, as evidenced by the ATP-III, patients with very-high TG levels  
10 were considered fundamentally different from patients with borderline-high or high TGs from a  
11 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

12 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride  
13 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In  
14 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at  
15 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular  
16 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).  
17 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels  
18 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by  
19 decreasing triglycerides), as required by the independent claims of the asserted patents, and  
20 therefore cannot anticipate the independent claim of the ‘446 Patent.

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22 <sup>2793</sup> ATP III at 3335; *See also* Section III.

23 <sup>2794</sup> *Id.*

24 <sup>2795</sup> *Id.*

<sup>2796</sup> *Id.*

1 (3) WO '118 Does Not Describe the Claimed Pharmaceutical  
2 Composition or its Specific Administration

3 WO '118 further does not anticipate the claims of the '446 patent because it does not  
4 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as  
5 claimed, it cannot anticipate oral administration to the claimed "subject."

6 WO '118 additionally cannot anticipate the claims of the '446 patent because it does not  
7 disclose administering the pharmaceutical composition at a dose of about 4g per day.  
8 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is  
9 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which  
10 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more  
11 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8  
12 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is  
13 not particularly limited as long as the intended effect, preventing the occurrence of  
14 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose  
15 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be  
16 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no  
17 working examples, data or other reference in WO '118 indicating that any subject (much less  
18 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the  
19 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

20 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of  
21 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The  
22 court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic  
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1 range of 330 to 450 °C,<sup>2797</sup> and therefore failed to anticipate the claimed range. The court in  
2 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate  
3 the patent’s claimed range of 0.1 to 5.0 percent.<sup>2798</sup> The court explained that “although there is a  
4 slight overlap, no reasonable fact finder could determine that this overlap describes the entire  
5 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are  
6 different, not the same. . . . Thus, there is no anticipation.”<sup>2799</sup> Similarly, although there may be  
7 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘446  
8 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range  
9 claimed by the ‘446 patent does not fall within WO ‘118’s preferred range. Defendants  
10 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,  
11 the example indicates that up to 900 mg of the EPA composition could be used three times per  
12 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘446  
13 patent and cannot anticipate the independent claim of the ‘446 Patent.

14 WO ‘118 further does not anticipate the claims of the ‘446 patent because it does not  
15 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a  
16 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.  
17 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high  
18 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and  
19 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or  
20 higher, and still more preferably 96.5% by weight or higher.”<sup>2800</sup> Therefore, WO ‘118 discloses

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22 <sup>2797</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>2798</sup> *Id.*

23 <sup>2799</sup> *Id.*

24 <sup>2800</sup> WO ‘118 at 22.



1 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total  
2 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed  
3 generic range for the EPA composition in the claimed pharmaceutical composition.

4 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the  
5 . . . range claimed in the” patent is insufficient for anticipation.<sup>2801</sup> In *Atofina*, the prior art  
6 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a  
7 range between 330 and 450 degrees. The court explained that this slight overlap “is not  
8 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>2802</sup> and therefore failed  
9 to anticipate the claimed range.<sup>2803</sup> The court in *Atofina* also found that a prior art disclosure of a  
10 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0  
11 percent.<sup>2804</sup> The court explained that “although there is a slight overlap, no reasonable fact finder  
12 could determine that this overlap describes the entire claimed range with sufficient specificity to  
13 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no  
14 anticipation.”<sup>2805</sup>

15 Similarly, although there may be some overlap between the E-EPA content disclosed by  
16 WO ‘118 and the ranges claimed by the ‘446 patent, WO ‘118 does not specifically highlight the  
17 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a  
18 critical factor of the invention disclosed in the ‘446 patent. Therefore, WO ‘118’s broad  
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21 <sup>2801</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

22 <sup>2802</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>2803</sup> *Atofina*, 441 F.3d at 1000.

24 <sup>2804</sup> *Id.*

<sup>2805</sup> *Id.*

1 disclosure of the E-EPA content in its invention does not describe the claimed range with  
2 sufficient specificity and cannot anticipate the independent claim of the '446 patent.

3 WO '118 is additionally insufficient for anticipation because it does not expressly  
4 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118  
5 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is  
6 DHA-E."<sup>2806</sup> The disclosure goes on to state that the composition of the invention is preferably  
7 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed  
8 pharmaceutical composition is a critical factor of the invention disclosed in the '446 patent.

9 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed  
10 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.  
11 There is no express teaching or guidance directing the person of ordinary skill in the art to the  
12 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no  
13 difference between the use of EPA or DHA in its invention, cannot anticipate the independent  
14 claim of the '446 patent.

15 Defendants contend that Plaintiffs are estopped from arguing there is any material  
16 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants  
17 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing  
18 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is  
19 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and  
20 Defendants have cited no authority to support their position suggesting the contrary. The  
21 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases  
22 and are not co-extensive. Accordingly, plaintiffs are not estopped.

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<sup>2806</sup> WO '118 at 22.

1 In the same paragraph containing their allegation of estoppel, Defendants also quote from  
2 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their  
3 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these  
4 statements form the basis for any theory of estoppel. To the extent that Defendants quote  
5 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The  
6 quoted statements do not identify any recited claim element, including the specific  
7 pharmaceutical composition, the recited patient population, administration in the manner  
8 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from  
9 the quoted statements.

10 (4) WO '118 Does Not Describe the Dependent Claims

11 Defendants fail to address any of the claim elements of the dependent claims.  
12 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail  
13 to set forth any meaningful basis for concluding that WO '118 teaches these elements.  
14 Defendants further argue that "aspects of the claims relating to effects that are to be achieved by  
15 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to  
16 no patentable weight." To the extent the recited claim elements relate to the administration step,  
17 the dosage form or characteristics of the treated subject and the specific effect produced by the  
18 claimed method, Defendants' contentions that the claim limitations are inherent properties of  
19 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO  
20 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.  
21 Defendants have not met the burden to establish anticipation with the naked assertion that the  
22 effects are inherent, natural properties of EPA.

23 Further, Defendants entirely fail to prove that inherently discloses the recited claim  
24 limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot

1 inherently anticipate as a matter of law.”<sup>2807</sup> “[A]nticipation by inherent disclosure is appropriate  
2 only when the reference discloses prior art that must *necessarily* include the unstated  
3 limitation.”<sup>2808</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
4 possibly present’ in the prior art.”<sup>2809</sup> Defendants fail to show that WO ‘118 “*necessarily*” meets  
5 the recited claim elements relating to the administration step, the dosage form or characteristics  
6 of the treated subject and the specific effect produced by the claimed method *every time*. WO  
7 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total  
8 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in  
9 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,  
10 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and  
11 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim  
12 elements.

### 13 3. The Claims of the ‘446 Patent Would Not Have Been Obvious In 14 Light of the Asserted References

15 Defendants identify 77 separate references that it asserts somehow render the claims of  
16 the ‘446 Patent obvious.<sup>2810</sup> Defendants fail to demonstrate by clear and convincing evidence  
17 that any of these references, alone or in combination, would render obvious any claims of the  
18 ‘446 Patent. Defendants’ arguments rely on hindsight by impermissibly using the blueprint of  
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21 <sup>2807</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

22 <sup>2808</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 <sup>2809</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 <sup>2810</sup> Defendants’ Joint Invalidity Contentions at 13-25.

1 the '446 Patent itself to guide its combination of references.<sup>2811</sup> Defendants chart a laundry list  
2 of 77 separate references, without explanation. Defendants' disclosures do not comply with  
3 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly  
4 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs  
5 cannot respond to undisclosed combinations and arguments.<sup>2812</sup>

6 Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions,  
7 Plaintiffs have discerned and will specifically respond to the following alleged prior art  
8 combinations:

- 9 • 1) “. . .the asserted claims of the '446 patent would have been obvious over the  
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
11 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in  
12 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori  
13 2000.”
- 14 • 2) “. . .the asserted claims of the '446 patent would have been obvious over the  
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
16 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,  
17 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori  
18 2000 and/or Maki.”
- 19 • 3) “. . .the asserted claims of the '446 patent would have been obvious over the  
20 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
21 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view  
22 of Satoh or Shinozaki in further view of Contacos.”
- 23 • 4) “. . . the asserted claims of the '446 patent would have been obvious over WO '118  
24 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the  
Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”

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20 <sup>2811</sup> *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention  
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is  
obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 <sup>2812</sup> This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,  
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for  
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the  
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that  
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to  
rely on undisclosed or insufficiently disclosed references or argument.

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- 2 • 5) “. . . the asserted claims of the ’446 patent are obvious over WO ’118, WO ’900,  
3 Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of  
4 Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view  
5 of Katayama, Matsuzawa and/or Takaku.”

6 A patent claim is invalid “if the differences between the subject matter sought to be  
7 patented and the prior art are such that the subject matter as a whole would have been obvious at  
8 the time the invention was made to a person having ordinary skill in the art.”<sup>2813</sup> Obviousness is  
9 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,  
10 (2) the scope and content of the prior art, and (3) the differences between the prior art and the  
11 claims at issue.<sup>2814</sup>

12 In evaluating obviousness, each prior art reference must be evaluated for all that it  
13 teaches, including the portions that would lead away from the claimed invention.<sup>2815</sup> Indeed, any  
14 teaching in the art that points away from the claimed invention must be considered.<sup>2816</sup> A  
15 reference teaches away if a person of ordinary skill, upon reading the reference, would be  
16 discouraged from following the path set out in the reference, or would be led in a direction  
17 divergent from the path that was taken by the applicant.<sup>2817</sup> For instance, a reference teaches  
18 away if it suggests that the line of development flowing from the reference’s disclosure is  
19 unlikely to be productive of the result sought by the applicant.<sup>2818</sup>

20 <sup>2813</sup> 35 U.S.C. § 103(a).

21 <sup>2814</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

22 <sup>2815</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2816</sup> *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

24 <sup>2817</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

<sup>2818</sup> *Id.*

1 In order to find obviousness based on a combination of references, there must be some  
2 rationale for combining the references in the way claimed that is separate and apart from the  
3 hindsight provided by the patented invention itself.<sup>2819</sup> The law prohibits an obviousness  
4 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art  
5 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of  
6 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed  
7 invention.”<sup>2820</sup> “The invention must be viewed not after the blueprint has been drawn by the  
8 inventor, but as it would have been perceived in the state of the art that existed at the time the  
9 invention was made.”<sup>2821</sup>

10 “The determination of obviousness is made with respect to the subject matter as a whole,  
11 not separate pieces of the claim.”<sup>2822</sup> “[A] patent composed of several elements is not proved  
12 obvious merely by demonstrating that each of its elements was, independently, known in the  
13 prior art.”<sup>2823</sup> “This is so because inventions in most, if not all, instances rely upon building  
14 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations  
15 of what, in some sense, is already known.”<sup>2824</sup>

16 Accordingly, it is improper to pick and choose isolated elements from the prior art and  
17 combine them so as to yield the invention<sup>2825</sup> or to modify a prior art reference in a way that

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19 <sup>2819</sup> *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

20 <sup>2820</sup> *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

21 <sup>2821</sup> *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

22 <sup>2822</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

23 <sup>2823</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

24 <sup>2824</sup> *KSR*, 550 U.S. at 418-419.

<sup>2825</sup> *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

1 “would destroy the fundamental characteristics of that reference.”<sup>2826</sup> Moreover, a combination  
2 is not obvious where “it would be impossible to apply these teachings [of the secondary  
3 reference] to the [primary reference] without entirely changing the basic mechanism and  
4 procedure thereof,”<sup>2827</sup> or where the proposed combination requires “material and radical  
5 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the  
6 prior art device.<sup>2828</sup> Furthermore, it is improper “to modify the secondary reference before it is  
7 employed to modify the primary reference” in assessing obviousness.<sup>2829</sup>

8 Further, a party asserting obviousness in view of a combination of prior art disclosures  
9 must show that a person of ordinary skill in the relevant field had an “apparent reason” to  
10 combine the elements in the manner claimed<sup>2830</sup> and “a reasonable expectation of success.”<sup>2831</sup>

11 For chemical compounds, there must have been a reason both to select the prior art  
12 compound “most promising to modify” and to make the necessary changes to arrive at the  
13 claimed compound.<sup>2832</sup> This protects against the use of hindsight to pick through the prior art  
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15 <sup>2826</sup> *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

16 <sup>2827</sup> *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

17 <sup>2828</sup> *Id.* at 88.

18 <sup>2829</sup> *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

19 <sup>2830</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 <sup>2831</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

23 <sup>2832</sup> *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–  
24 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*  
*Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).



1 based solely on structural similarity to the claimed compound.<sup>2833</sup> Any assertion of an “apparent  
2 reason” must find a basis in the factual record.<sup>2834</sup>

3 The “reasonable expectation of success” for a chemical compound must be of all of a  
4 claimed compound’s relevant properties,<sup>2835</sup> including those discovered after the patent was filed  
5 or even issued.<sup>2836</sup> “The basic principle behind this rule is straight-forward—that which would  
6 have been surprising to a person of ordinary skill in a particular art would not have been  
7 obvious.”<sup>2837</sup> Any assertion of a “reasonable expectation of success” must find a basis in the  
8 factual record.<sup>2838</sup>

9  
10 <sup>2833</sup> *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at \*14. *Accord In re Vaidyanathan*, 381. 985, 994  
11 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.  
12 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.  
13 2002).

12 <sup>2834</sup> *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions  
13 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to  
14 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the  
15 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at  
16 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the  
17 invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed  
18 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438  
19 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in  
20 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that  
21 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
22 motivated to resolve citalopram in June 1988”).

17 <sup>2835</sup> *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success  
18 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .  
19 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of  
20 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d  
21 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the  
22 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of  
23 pharmacological properties that it possesses.”).

20 <sup>2836</sup> *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at  
21 908.

22 <sup>2837</sup> *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,  
23 such as chemistry, where minor changes in a product or process may yield substantially different results.”).

23 <sup>2838</sup> *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Aptex argues that the district court applied an incorrect  
24 inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were

1 In an obviousness determination, any objective indicia of nonobviousness must be taken  
2 into account.<sup>2839</sup> An objective indicium is any “event[] proved to have actually happened in the  
3 real world” that evidences the nonobvious nature of the invention.<sup>2840</sup> The existence of an  
4 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or  
5 surprising results, expressions of skepticism, industry praise, commercial success, and copying  
6 are classical indicia of nonobviousness.<sup>2841</sup> These factual inquiries “guard against slipping into  
7 use of hindsight,”<sup>2842</sup> and “may often be the most probative and cogent evidence of  
8 nonobviousness.”<sup>2843</sup>

9 Also, as with assertions of anticipation, in order for an invention to be obvious, it must  
10 have been fully “in possession” of the public—which requires that the claimed invention have  
11 been enabled.<sup>2844</sup>

12  
13 \_\_\_\_\_  
14 unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general  
15 knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955  
16 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.  
17 However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly  
18 expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re*  
19 *May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a  
20 substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

21 <sup>2839</sup> *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

22 <sup>2840</sup> *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

23 <sup>2841</sup> *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*  
24 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750  
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

<sup>2842</sup> *Graham*, 383 U.S. at 36.

<sup>2843</sup> *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*  
*Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

<sup>2844</sup> *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for  
obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,  
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for  
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound  
itself is in the possession of the public.”).

1 A element-by-element analysis, identifying each limitation of each asserted claim that is  
2 absent from the prior art, is provided below, and also provided at Exhibit F. The contentions  
3 below are incorporated by reference into Exhibit F, and vice-versa.

4 a) General Overview

5 Defendants fail to provide a single prior art reference that discloses administration of the  
6 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population  
7 ( $\geq 500$  mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,  
8 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying  
9 degrees of purity, in a wide range of doses and administration periods, to subjects who have  
10 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance  
11 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo  
12 controlled studies are considered the “gold standard” of clinical studies. Studies involving the  
13 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot  
14 distinguish between the effect of the placebo from that of the active agent. Studies which  
15 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the  
16 independent effects of EPA and DHA.<sup>2845</sup> Inconsistency in dosages and administration periods  
17 and variations in the administered fatty acid compositions also complicate the interpretation of  
18 the results and limit the application of these studies.

19 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with  
20 very high TGs together with patients with high and borderline high TGs indicates that there is no  
21 medical difference in responsiveness to treatment among the groups of people.”<sup>2846</sup> Defendants  
22

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23 <sup>2845</sup> Mori 2006 at 96.

24 <sup>2846</sup> Defendants’ Joint Invalidity Contentions at 440 (*see* FN 76).

1 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-  
2 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in  
3 patients with high triglycerides ( $\geq 200$  mg/dL and  $< 500$  mg/dL) who were also on statin therapy.  
4 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g  
5 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG  
6 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that  
7 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.<sup>2847</sup> In  
8 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were  
9 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use  
10 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a  
11 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the  
12 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to  
13 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.  
14 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical  
15 difference in responsiveness to treatment between the very-high TG patient population and lower  
16 TG patient populations merely because there was possibly one patient with baseline TG levels of  
17 at least 500 mg/dL.

18 As discussed above in Section III, patients with very-high TG levels were considered  
19 fundamentally different from patients with borderline-high or high TGs from a clinical,  
20 regulatory, and therapeutic perspective.<sup>2848</sup> Clinically, the authoritative guidance to physicians

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22 <sup>2847</sup> FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6  
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been  
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline  
TG values < 500 mg/dL).

24 <sup>2848</sup> See Bays Jan. 8, 2012 Decl., ¶ 20.

1 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III  
2 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;  
3 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients  
4 was atherosclerosis, while the primary risk faced by very-high TG patients was acute  
5 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for  
6 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for  
7 very-high TG patients was TG reduction. This distinction between patients with borderline-  
8 high/high TG levels and patients with very high TG levels is also observed on the regulatory  
9 level. The FDA recognized the different clinical status of the very-high TG population by  
10 approving some drugs specifically for the very-high TG group without granting treatment  
11 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).<sup>2849</sup>

12 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the  
13 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the  
14 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known  
15 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the  
16 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG  
17 level of the patient receiving treatment.

18 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but  
19 *increase* LDL-C in very-high TG patients.<sup>2850</sup> The fibrate, Tricor (fenofibrate), for example,  
20 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)<sup>2851</sup>

21  
22 <sup>2849</sup> See Bays Jan. 8, 2012 Decl., ¶ 22.

23 <sup>2850</sup> See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain  
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

24 <sup>2851</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).<sup>2852</sup> In  
 2 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-  
 3 significant increase in LDL-C was observed.<sup>2853</sup> In patients with very-high TGs (mean baseline  
 4 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).<sup>2854</sup> Similar  
 5 results were seen with the administration of Lopid (gemfibrozil).<sup>2855</sup> The differing effects of  
 6 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values  
 7 demonstrates how a person of ordinary skill at the time of the invention would have understood  
 8 that one could not simply assume that an observed effect of a TG-lowering agent on lipid  
 9 parameters in patients with normal, borderline-high or high TG levels would be the same in  
 10 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or  
 11 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with  
 12 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-  
 13 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean  
 14 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level  
 15 of 726 mg/dL) experience significantly increased LDL-C levels.

<b>Fibrate</b>	<b>Mean Baseline TG Value</b>	<b>TG</b>	<b>LDL-C</b>	<b>HDL-C</b>	<b>Total-C</b>
Tricor (fenofibrate) <sup>2856</sup>	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*

20 <sup>2852</sup> *Id.*

21 <sup>2853</sup> *Id.* See also, Trilipix Label at 27.

22 <sup>2854</sup> *Id.* See also, Trilipix Label at 27.

23 <sup>2855</sup> See *Otvos* at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); *Manttari* at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

24 <sup>2856</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

\* = p < 0.05 vs. Placebo

Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing lipid effects depending on the patient’s baseline TG level. When administered to patients with borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-C.<sup>2857</sup> It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.<sup>2858</sup> However, when administered to patients with very-high baseline TG levels, TGs were reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.<sup>2859</sup> Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>2860</sup>

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG

<sup>2857</sup> Chan 2002 I at 2379-81.

<sup>2858</sup> *Id.*; See also, Westphal at 918.

<sup>2859</sup> See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

<sup>2860</sup> See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”)

1 levels ( $\geq 500$  mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They  
2 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when  
3 the normal, borderline-high or high TG patient populations were administered omega-3 fatty  
4 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was  
5 expected as a natural consequence of lowering TGs. A person of ordinary skill would have  
6 considered the rise in LDL-C to be a direct consequence of TG lowering through increased  
7 VLDL particle conversion.<sup>2861</sup> Because normal to high TG patients did not have the large  
8 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not  
9 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree  
10 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,  
11 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the  
12 highest baseline TG levels<sup>2862</sup> and did not increase for patients with lower TG levels. Therefore,  
13 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,  
14 borderline-high or high TG patients was *expected*.

15 Defendants contend that “a composition and its properties are inseparable, and therefore  
16 do not impart any additional patentability,” and that “all of the limitations regarding the  
17 properties of the ethyl EPA compound identified in the claims of the ‘446 patent are inherent to  
18 the compound when administered to a human subject.”<sup>2863</sup> Inherency may not supply a missing

19 \_\_\_\_\_  
20 <sup>2861</sup> Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class  
21 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels  
22 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during  
treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some  
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the  
decrease in VLDL.”).

23 <sup>2862</sup> Bays 2008 I at 400-402.

24 <sup>2863</sup> Defendants’ Joint Invalidity Contentions at 441.



1 claim limitation in an obviousness analysis unless the inherency would have been obvious to one  
2 of ordinary skill in the art.<sup>2864</sup> Obviousness is based on what is *known* in the art at the time of the  
3 invention.<sup>2865</sup> It was not known or reasonably expected at the time of the claimed invention that  
4 purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL), would not  
5 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and  
6 Apo-B necessarily present, or the natural result of the combination of elements explicitly  
7 disclosed by the prior art.<sup>2866</sup> Therefore, inherency does not supply the missing claim elements  
8 in the prior art cited by Defendants.

9 Defendants argue that the claims of the ‘446 patent which contain “a limiting clause, such  
10 as ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step positively  
11 recited and therefore are not elements.<sup>2867</sup> This is incorrect. “There is nothing inherently wrong  
12 with defining some part of an invention in functional terms.”<sup>2868</sup> When a clause “states a  
13 condition that is material to patentability, it cannot be ignored in order to change the substance of  
14 the invention.”<sup>2869</sup> The claim term “to effect” acts as a positive limitation if the term represents

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17 <sup>2864</sup> See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .  
18 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an  
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of  
elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere  
19 fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

20 <sup>2865</sup> *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.  
Obviousness cannot be predicated on what is unknown.”).

21 <sup>2866</sup> See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 <sup>2867</sup> Defendants’ Joint Invalidity Contentions at 441.

23 <sup>2868</sup> See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 <sup>2869</sup> *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

1 “unexpected and improved effects of administration of the claimed compound.”<sup>2870</sup> In addition,  
2 the elements represent unexpected and improved effects of administration of purified EPA,  
3 because a person of ordinary skill would not have expected no substantial increase in LDL-C or  
4 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the  
5 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded  
6 patentable weight.

7 b) Identification of Claim Elements Absent from Each Item of Prior  
8 Art

9 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.  
10 Where a limitation is absent from any Independent Claim, that limitation is absent from all  
11 asserted claims, and that analysis is incorporated by reference into each dependent claim. For  
12 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted  
13 claims is not a concession that such limitation is present in the reference. By discussing  
14 Defendants’ analysis of the “limitations” in the claims, Plaintiffs do not concede that Defendants  
15 have appropriately divided the claim language for any purpose.

16 (1) WO ‘118

17 WO ‘118 discloses a composition containing EPA-E for preventing the occurrence of  
18 cardiovascular events in multiple risk patients.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
20 ‘118 disclose or suggest elements of the ‘446 Claims. The cited portions of WO ‘118 do not  
21 disclose or suggest these elements at least because they do not disclose or suggest administration  
22 of EPA with the recited purity to a subject with the recited very high TG levels. The cited

23 \_\_\_\_\_  
24 <sup>2870</sup> AstraZeneca AB v. Dr. Reddy’s Labs., Ltd., No. CIV.A.05-5553 JAP, 2010 WL 1981790, at \*11–12 (D.N.J.  
May 18, 2010).

1 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition  
2 with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not  
3 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
4 LDL-C based on a comparison to placebo control.

5 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), WO '118  
6 does not disclose or suggest a subject with the recited very high TG level. WO '118 also does  
7 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids  
8 compositions or dosage. WO '118 further does not disclose or suggest a method to effect the  
9 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
10 control.

11 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
12 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
13 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
14 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
15 Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
16 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
17 to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
18 subject with the claimed TG levels based on a comparison to placebo control. With regards to  
19 claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

20 (2) WO '900

21 WO '900 describes methods for obtaining EPA-rich compositions.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
23 '900 disclose or suggest elements of the '446 Claims. The cited portions of WO '900 do not  
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
2 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition  
3 with the recited fatty acid dosage or administration period. The cited portions of WO '900  
4 further do not disclose or suggest a method to effect the recited TG reduction without  
5 substantially increasing LDL-C based on a comparison to placebo control.

6 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), WO '900  
7 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does  
8 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 dosage or administration period. WO '900 further does not disclose or suggest a method to  
10 effect the recited TG reduction without substantially increasing LDL-C based on a comparison to  
11 placebo control.

12 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
13 having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose  
14 or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this  
15 reference fails to disclose or suggest the recited reduction in TG without substantially increasing  
16 LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

17 With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in  
18 Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo  
19 control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction  
20 in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

21 With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.  
22  
23  
24

1 (3) Contacos

2 Contacos describes a study designed to determine the safety and efficacy of a statin  
3 (pravastatin) combined with fish oil either alone or in combination, for the management of  
4 patients with mixed hyperlipidemia.

5 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
6 Contacos disclose or suggest elements of the '446 Claims. The cited portions of Contacos do not  
7 disclose or suggest these elements at least because they do not disclose or suggest administration  
8 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
9 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition  
10 with the recited fatty acid compositions, dosage, or administration period. The cited portions of  
11 Contacos further do not disclose or suggest a method of administering the claimed  
12 pharmaceutical composition to effect the recited TG reduction without substantially increasing  
13 LDL-C based on a comparison to placebo control.

14 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Contacos  
15 does not disclose or suggest a subject with the recited very high TG level. Contacos also does  
16 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
17 compositions, dosage, or administration period. Contacos further does not disclose or suggest a  
18 method of administering the claimed pharmaceutical composition to effect the recited TG  
19 reduction without substantially increasing LDL-C based on a comparison to placebo control.

20 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
21 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
22 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
23 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
24 placebo control. With respect to Claim 6, this reference fails to disclose or suggest the

1 administration of the claimed pharmaceutical composition to effect the recited reduction in  
2 Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this  
3 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
4 composition to effect the recited reduction in VLDL-C based on a comparison to placebo  
5 control. With regards to claims 8-11, this reference fails to disclose or suggest the recited  
6 capsule dosage.

7 (4) Grimsgaard

8 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design  
9 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,  
10 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG  
11 levels.

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
13 Grimsgaard disclose or suggest elements of the '446 Claims. The cited portions of Grimsgaard  
14 do not disclose or suggest these elements at least because they do not disclose or suggest  
15 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
16 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical  
17 composition with the recited administration period. The cited portions of Grimsgaard further do  
18 not disclose or suggest a method to effect the recited TG reduction without substantially  
19 increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo  
20 control.

21 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Grimsgaard  
22 does not disclose or suggest a subject with the recited very high TG level. Grimsgaard also does  
23 not disclose or suggest the claimed pharmaceutical composition with the recited administration  
24 period. Grimsgaard further does not disclose or suggest a method to effect the recited TG

1 reduction without substantially increasing LDL-C in the subject with the claimed TG levels  
2 based on a comparison to placebo control.

3 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
4 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
5 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
6 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
7 Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
8 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
9 to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
10 subject with the claimed TG levels based on a comparison to placebo control. With regards to  
11 claims 8-10, this reference fails to disclose or suggest the recited capsule dosage.

12 (5) Hayashi

13 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for  
14 8 weeks. The purity of the composition is not reported. The study was not placebo controlled  
15 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride  
16 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220  
17 mg/dl.

18 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the  
19 '446 patent claims. For example, the cited portions of Hayashi do not disclose or suggest  
20 administration of EPA with the recited purity to a subject with the recited very high TG levels  
21 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject  
22 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or  
23 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or  
24 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the

1 recited TG reduction without substantially increasing LDL-C in a subject with the recited very  
2 high TG levels.

3 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Hayashi  
4 does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not  
5 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
6 compositions or dosage. Hayashi further does not disclose or suggest a method to effect the  
7 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
8 control.

9 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
10 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
11 disclose or suggest the recited reduction in TG without substantially increasing LDL-C based on  
12 a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or  
13 suggest the recited reduction in Apolipoprotein B based on a comparison to placebo control.  
14 With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in  
15 VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference  
16 fails to disclose or suggest the recited capsule dosage.

17 (6) Katayama

18 Katayama was directed to an investigation of the safety and efficacy of Epadel during  
19 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,  
20 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and  
21 was not placebo controlled.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
23 Katayama disclose or suggest elements of the '446 Claims. The cited portions of Katayama do  
24 not disclose or suggest these elements at least because they do not disclose or suggest



1 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
2 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical  
3 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama  
4 further do not disclose or suggest a method to effect the recited TG reduction without  
5 substantially increasing LDL-C based on a comparison to placebo control.

6 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Katayama  
7 does not disclose or suggest a subject with the recited very high TG level. Katayama also does  
8 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or dosage. Katayama further does not disclose or suggest a method to effect the  
10 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
11 control.

12 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
13 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
14 disclose or suggest the recited reduction in TG without substantially increasing LDL-C based on  
15 a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or  
16 suggest the recited reduction in Apolipoprotein B based on a comparison to placebo control.  
17 With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in  
18 VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference  
19 fails to disclose or suggest the recited capsule dosage.

20 (7) Leigh-Firbank

21 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle  
22 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank  
23 does not administer EPA of the purity recited in the claims.  
24

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
2 Leigh-Firbank disclose or suggest elements of the '446 Claims. The cited portions of Leigh-  
3 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest  
4 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
5 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed  
6 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration  
7 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of  
8 administering the claimed pharmaceutical composition to effect the recited TG reduction without  
9 substantially increasing LDL-C based on a comparison to placebo control.

10 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Leigh-  
11 Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-  
12 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the  
13 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not  
14 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
15 the recited TG reduction without substantially increasing LDL-C based on a comparison to  
16 placebo control.

17 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
18 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
19 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
20 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
21 placebo control. With respect to Claim 6, this reference fails to disclose or suggest the  
22 administration of the claimed pharmaceutical composition to effect the recited reduction in  
23 Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this  
24

1 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
2 composition to effect the recited reduction in VLDL-C based on a comparison to placebo  
3 control. With regards to claims 8-11, this reference fails to disclose or suggest the recited  
4 capsule dosage.

5 (8) Lovaza PDR

6 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
8 Lovaza PDR disclose or suggest elements of the '446 Claims. The cited portions of the Lovaza  
9 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
10 administration of EPA with the recited purity to a subject with the recited very high TG levels.

11 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed  
12 pharmaceutical composition with the recited fatty acid composition or administration period.

13 The cited portions of the Lovaza PDR further do not disclose or suggest a method of  
14 administering the claimed pharmaceutical composition to effect the recited TG reduction without  
15 substantially increasing LDL-C based on a comparison to placebo control.

16 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), the Lovaza  
17 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
18 acid compositions or administration period. The Lovaza PDR further does not disclose or  
19 suggest a method of administering the claimed pharmaceutical composition to effect the recited  
20 TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

21 Further, with respect to Claims 4 and 5, this reference fails to disclose or suggest the  
22 administration of the claimed pharmaceutical composition to effect the recited reduction in TG  
23 without substantially increasing LDL-C based on a comparison to placebo control. With respect  
24 to Claim 6, this reference fails to disclose or suggest the administration of the claimed

1 pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a  
2 comparison to placebo control. With respect to Claim 7, this reference fails to disclose or  
3 suggest the administration of the claimed pharmaceutical composition to effect the recited  
4 reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11,  
5 this reference fails to disclose or suggest the recited capsule dosage.

6 (9) Maki

7 Maki administered 1.52g/day DHA supplements to patients with below-average levels of  
8 HDL-C. Maki does not administer EPA of the purity recited in the claims.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki  
10 disclose or suggest elements of the '446 Claims. The cited portions of Maki do not disclose or  
11 suggest these elements at least because they do not disclose or suggest administration of EPA  
12 with the recited purity to a subject with the recited very high TG levels. The cited portions of  
13 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited  
14 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do  
15 not disclose or suggest a method of administering the claimed pharmaceutical composition to  
16 effect the recited TG reduction without substantially increasing LDL-C based on a comparison to  
17 placebo control.

18 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Maki does  
19 not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose  
20 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,  
21 dosage, or administration period. Maki further does not disclose or suggest a method of  
22 administering the claimed pharmaceutical composition to effect the recited TG reduction without  
23 substantially increasing LDL-C based on a comparison to placebo control.

1 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
2 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
3 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
4 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
5 placebo control. With respect to Claim 6, this reference fails to disclose or suggest the  
6 administration of the claimed pharmaceutical composition to effect the recited reduction in  
7 Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this  
8 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
9 composition to effect the recited reduction in VLDL-C based on a comparison to placebo  
10 control. With regards to claims 8-11, this reference fails to disclose or suggest the recited  
11 capsule dosage.

12 (10) Matsuzawa

13 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-  
14 term use in the treatment of the disease and was not placebo controlled.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
16 Matsuzawa disclose or suggest elements of the '446 Claims. The cited portions of Matsuzawa  
17 do not disclose or suggest these elements at least because they do not disclose or suggest  
18 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
19 The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical  
20 composition with the recited fatty acid compositions or dosage. The cited portions of  
21 Matsuzawa further do not disclose or suggest a method of administering the claimed  
22 pharmaceutical composition to effect the recited TG reduction without substantially increasing  
23 LDL-C based on a comparison to placebo control.

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1 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Matsuzawa  
2 does not disclose or suggest a subject with the recited very high TG level. Matsuzawa also does  
3 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
4 compositions or dosage. Matsuzawa further does not disclose or suggest a method of  
5 administering the claimed pharmaceutical composition to effect the recited TG reduction without  
6 substantially increasing LDL-C based on a comparison to placebo control.

7 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
8 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
9 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
10 recited reduction in TG without substantially increasing LDL-C based on a comparison to  
11 placebo control. With respect to Claim 6, this reference fails to disclose or suggest the  
12 administration of the claimed pharmaceutical composition to effect the recited reduction in  
13 Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this  
14 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
15 composition to effect the recited reduction in VLDL-C based on a comparison to placebo  
16 control. With regards to claims 8-11, this reference fails to disclose or suggest the recited  
17 capsule dosage.

18 (11) Mori 2000

19 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum  
20 lipids and lipoproteins, glucose and insulin in humans.

21 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
22 2000 disclose or suggest elements of the '446 Claims. The cited portions of Mori 2000 do not  
23 disclose or suggest these elements at least because they do not disclose or suggest administration  
24 of EPA with the recited purity to a subject with the recited very high TG levels. The cited

1 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition  
2 with the recited dosage or administration period. The cited portions of Mori 2000 further do not  
3 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
4 LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

5 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Mori 2000  
6 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 also does  
7 not disclose or suggest the claimed pharmaceutical composition with the recited dosage or  
8 administration period. Mori 2000 further does not disclose or suggest a method to effect the  
9 recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG  
10 levels based on a comparison to placebo control.

11 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
12 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
13 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
14 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
15 Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
16 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
17 to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
18 subject with the claimed TG levels based on a comparison to placebo control. With regards to  
19 claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

20 (12) Mori 2006

21 Mori 2006 is a review which reports data from clinical trials which compared the  
22 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

23 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
24 2006 disclose or suggest elements of the '446 Claims. The cited portions of Mori 2006 do not

1 disclose or suggest these elements at least because they do not disclose or suggest administration  
2 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
3 portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition  
4 with the recited fatty acid dosage or administration period. The cited portions of Mori 2006  
5 further do not disclose or suggest a method to effect the recited TG reduction without  
6 substantially increasing LDL-C based on a comparison to placebo control.

7 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Mori 2006  
8 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does  
9 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
10 dosage or administration period. Mori 2006 further does not disclose or suggest a method to  
11 effect the recited TG reduction without substantially increasing LDL-C based on a comparison to  
12 placebo control.

13 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
14 having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose  
15 or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this  
16 reference fails to disclose or suggest the recited reduction in TG without substantially increasing  
17 LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

18 With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in  
19 Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo  
20 control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction  
21 in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

22 With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.  
23  
24



1 (13) Nozaki

2 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The  
3 purity of the composition is reported as 90%. The study was not placebo controlled and was  
4 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165  
5 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG  
6 patient population.

7 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the  
8 '446 patent claims. For example, the cited portions of Nozaki do not disclose or suggest  
9 administration of EPA with the recited purity to a subject with the recited very high TG levels  
10 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do  
11 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
12 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a  
13 method to effect the recited TG reduction without substantially increasing LDL-C in a subject  
14 with the recited very high TG levels.

15 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the  
16 '446 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least  
17 because they do not disclose or suggest administration of EPA with the recited purity to a subject  
18 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The  
19 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical  
20 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki  
21 further do not disclose or suggest a method to effect the recited TG reduction without  
22 substantially increasing LDL-C.

23 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Nozaki  
24 does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not

1 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions or dosage. Nozaki further does not disclose or suggest a method to effect the  
3 recited TG reduction without substantially increasing LDL-C based on a comparison to placebo  
4 control.

5 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
6 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
7 disclose or suggest the recited reduction in TG without substantially increasing LDL-C based on  
8 a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or  
9 suggest the recited reduction in Apolipoprotein B based on a comparison to placebo control.  
10 With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in  
11 VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference  
12 fails to disclose or suggest the recited capsule dosage.

13 (14) Omacor PDR

14 The Omacor PDR is the Physicians' Desk Reference describing Lovaza.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
16 Omacor PDR disclose or suggest elements of the '446 Claims. The cited portions of the Omacor  
17 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
18 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
19 The cited portions of the Omacor PDR further do not disclose or suggest the claimed  
20 pharmaceutical composition with the recited fatty acid composition or administration period.  
21 The cited portions of the Omacor PDR further do not disclose or suggest a method of  
22 administering the claimed pharmaceutical composition to effect the recited TG reduction without  
23 substantially increasing LDL-C based on a comparison to placebo control.

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1 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), the Omacor  
2 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
3 acid compositions or administration period. The Omacor PDR further does not disclose or  
4 suggest a method of administering the claimed pharmaceutical composition to effect the recited  
5 TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

6 Further, with respect to Claims 4 and 5, this reference fails to disclose or suggest the  
7 administration of the claimed pharmaceutical composition to effect the recited reduction in TG  
8 without substantially increasing LDL-C based on a comparison to placebo control. With respect  
9 to Claim 6, this reference fails to disclose or suggest the administration of the claimed  
10 pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a  
11 comparison to placebo control. With respect to Claim 7, this reference fails to disclose or  
12 suggest the administration of the claimed pharmaceutical composition to effect the recited  
13 reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11,  
14 this reference fails to disclose or suggest the recited capsule dosage.

15 (15) Satoh

16 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
17 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
18 systemic inflammation.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
20 Satoh disclose or suggest elements of the '446 Claims. The cited portions of Satoh do not  
21 disclose or suggest these elements at least because they do not disclose or suggest administration  
22 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
23 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with  
24 the recited dosage. The cited portions of Satoh further do not disclose or suggest a method to

1 effect the recited TG reduction without substantially increasing LDL-C in the subject with the  
2 claimed TG levels based on a comparison to placebo control.

3 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Satoh does  
4 not disclose or suggest a subject with the recited very high TG level. Satoh also does not  
5 disclose or suggest the claimed pharmaceutical composition with the recited dosage. Satoh  
6 further does not disclose or suggest a method to effect the recited TG reduction without  
7 substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison  
8 to placebo control.

9 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
10 having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to  
11 disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the  
12 subject with the claimed TG levels based on a comparison to placebo control. With respect to  
13 Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in  
14 the subject with the claimed TG levels based on a comparison to placebo control. With respect  
15 to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
16 subject with the claimed TG levels based on a comparison to placebo control. With regards to  
17 claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

18 (16) Shinozaki

19 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and  
20 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

21 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
22 Shinozaki disclose or suggest elements of the '446 Claims. The cited portions of Shinozaki do  
23 not disclose or suggest these elements at least because they do not disclose or suggest  
24 administration of EPA with the recited purity to a subject with the recited very high TG levels.

1 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical  
2 composition with the recited dosage. The cited portions of Shinozaki further do not disclose or  
3 suggest a method to effect the recited TG reduction without substantially increasing LDL-C in  
4 the subject with the claimed TG levels based on a comparison to placebo control.

5 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Shinozaki  
6 does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does  
7 not disclose or suggest the claimed pharmaceutical composition with the recited dosage.  
8 Shinozaki further does not disclose or suggest a method to effect the recited TG reduction  
9 without substantially increasing LDL-C in the subject with the claimed TG levels based on a  
10 comparison to placebo control.

11 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
12 having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose  
13 or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this  
14 reference fails to disclose or suggest the recited reduction in TG without substantially increasing  
15 LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.  
16 With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in  
17 Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo  
18 control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction  
19 in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control.  
20 With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

21 (17) Takaku

22 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-  
23 term use and was not placebo controlled.

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
2 Takaku disclose or suggest elements of the '446 Claims. The cited portions of Takaku do not  
3 disclose or suggest these elements at least because they do not disclose or suggest administration  
4 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
5 portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition  
6 with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not  
7 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
8 the recited TG reduction without substantially increasing LDL-C based on a comparison to  
9 placebo control.

10 With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Takaku  
11 does not disclose or suggest a subject with the recited very high TG level. Takaku also does not  
12 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
13 compositions or dosage. Takaku further does not disclose or suggest a method of administering  
14 the claimed pharmaceutical composition to effect the recited TG reduction without substantially  
15 increasing LDL-C based on a comparison to placebo control.

16 Further, with respect to Claim 2, this reference fails to disclose or suggest the subject  
17 having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose  
18 or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this  
19 reference fails to disclose or suggest the recited reduction in TG without substantially increasing  
20 LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.  
21 With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in  
22 Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo  
23 control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction  
24

1 in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control.  
2 With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

3 c) The Prior Art Does Not Render the Claims Obvious

4 Defendants have not identified by clear and convincing evidence that the asserted claims  
5 of the '446 Patent would have been *prima facie* obvious in light of the references cited, either  
6 alone or in combination. As described above, none of the references discloses all of the elements  
7 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without  
8 explanation, and argue they somehow must be combined to render obvious the asserted claims.  
9 Where Defendants have failed to make disclosures with the specificity required by Local Patent  
10 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the  
11 claim elements at issue.

12 Defendants' contentions fail to disclose each and every element of the claims of the '446  
13 patent. Specifically, Defendants do not contend that the relied upon references disclose the  
14 following elements of Claim 1 (and therefore Claims 2-11): *administering the claimed*  
15 *pharmaceutical composition to the recited subject to effect a reduction in triglycerides without*  
16 *substantially increasing LDL-C based upon a comparison to placebo control.* Therefore,  
17 Defendants' prior art combinations cannot render the claims *prima facie* obvious.

18 Facts supporting the non-obviousness of the claims of the '446 patent are discussed in  
19 detail below. The objective indicia discussed in Section V.O further demonstrate that the '446  
20 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims  
21 would have been obvious.

22 (1) Defendants Do Not Demonstrate that the Independent  
23 Claim of the '446 Patent Would Have Been Obvious

24 (a) Defendants Do Not Demonstrate that a Person of  
Ordinary Skill in the Art Would Have Had Any

Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

- (i) The '446 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, Further in View of Nozaki and/or Hayashi and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '446 Patent, Defendants present a combination of seven references:

“the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000.”<sup>2871</sup> Defendants also present charts purporting to assert that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 61 separate references, they additionally do not identify any motivation for combining these references.<sup>2872, 2873</sup> Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent

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<sup>2871</sup> Defendants' Joint Invalidation Contentions at 435.

<sup>2872</sup> Defendants' bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as described in the references cited above in section V.B.2) in view of, at least, the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidation Contentions at 434-35.

<sup>2873</sup> Defendants' bare assertion that “the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,” and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure requirements of the Nevada Local Patent Rules. *See* Defendants' Joint Invalidation Contentions at 433.



1 reason” to combine must find a basis in the factual record.<sup>2874</sup> Defendants’ unsupported cobbling  
2 of selective disclosures represents hindsight reconstruction.<sup>2875</sup> Defendants’ contentions are no  
3 more than an assertion that certain claim elements were known in the prior art. Throughout their  
4 contentions, Defendants’ selectively cite to data points in a reference without considering other  
5 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
6 that it teaches.<sup>2876</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
9 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed  
10 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a  
11 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the  
12 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a  
13 significant increase in LDL-C levels in the very high TG patient population, for whom the  
14 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,  
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16 <sup>2874</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2875</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>2876</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce  
2 TG levels in adult patients with very-high ( $\geq 500$  mg/dL) TG levels.

3 The proposed combinations do not render the independent claim of the '446 Patent  
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
5 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza  
6 package insert specifically) during prosecution.<sup>2877</sup>

7 The analysis of the independent claim of the '446 Patent is incorporated into all asserted  
8 claims that depend from this Claim.

9 (a) A Person of Ordinary Skill Would  
10 Not Have Been Motivated to  
11 Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with Pure EPA

12 For an invention to be obvious, there must have been an "apparent reason" to make it.  
13 The subject matter of the '446 patent claims would not have been obvious in light of these  
14 references because a person of ordinary skill would not have been motivated to purify EPA or  
15 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
16 levels without an increase in LDL-C levels.

17 (i) Katayama and/or Matsuzawa  
18 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

19 Both Katayama and Matsuzawa are long term studies directed to an investigation of the  
20 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies

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22 <sup>2877</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the  
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
24 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").

1 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may  
2 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the  
3 art would not and could not attribute any observed effect (and the magnitude of that effect) to  
4 that of the drug. Any observed effect could be placebo dependent.<sup>2878</sup> As discussed above in  
5 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with  
6 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG  
7 patients because patients with higher TG levels had different lipid responses compared to  
8 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally  
9 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical  
10 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary  
11 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were  
12 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art  
13 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-  
14 high or high TG patients, was expected. At the priority date of the ‘446 patent, a person of  
15 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients  
16 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been  
17 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG  
18 lowering through increased VLDL particle conversion.

19 Defendants argue that these studies disclose known “clinical benefits” of administering  
20 pure EPA, lowering triglycerides without raising LDL-C.<sup>2879</sup> This is an incorrect

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22 <sup>2878</sup>See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a  
23 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a  
24 placebo-controlled study and why results compared only to baseline may be misleading.)

<sup>2879</sup> Defendants’ Joint Invalidity Contentions at 435-36.

1 characterization of these two studies. Katayama and Matsuzawa both were only designed to  
2 confirm the safety of long term treatment of Epadel and its ability to lower both serum total  
3 cholesterol and TG levels. They do just that. They do not discuss any purported “benefits”  
4 observed related to LDL-C. Defendants’ selective citation of LDL-C data from these references  
5 represents the improper use of hindsight bias. A person of ordinary skill would understand the  
6 focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels,  
7 and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does  
8 not mention LDL-C levels at all. Defendants’ characterization of Katayama and Matsuzawa as  
9 disclosing the lowering of TG levels without increasing LDL-C to be a “clinical benefit” is  
10 incorrect.<sup>2880</sup> The references don’t disclose or suggest that the LDL-C results obtained were a  
11 clinical benefit, nor would a person of ordinary skill view these references as teaching such a  
12 benefit for very-high TG patients.

13 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid  
14 effects. These studies fail to provide a head to head comparison of EPA versus DHA.  
15 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to  
16 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

17 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The  
18 purity of Epadel has varied over time and across different formulations of the product, therefore  
19 it is difficult to determine the purity of the version of Epadel used unless it is specified by the  
20 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the  
21 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and  
22 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference  
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24 <sup>2880</sup> Defendants’ Joint Invalidation Contentions at 435-136.

1 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.  
2 Nishikawa,<sup>2881</sup> published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.  
3 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite  
4 purity.<sup>2882</sup>

5 Further, Katayama and Matsuzawa were small studies conducted in only Japanese  
6 patients. These studies would not have been extrapolated to Western populations because the  
7 Japanese diet contains much more fish and has a number of other different attributes. The  
8 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In  
9 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where  
10 the patient population is exclusively Japanese cannot be generalized to other populations.<sup>2883</sup>  
11 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical  
12 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-  
13 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand  
14 that the Japanese respond differently to lipid lowering agents than Westerners.

15 Defendants rely on Katayama to demonstrate the "known clinical benefits of  
16 administering pure EPA - lowering triglycerides without raising LDL-C."<sup>2884</sup> However,  
17 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term  
18 treatment in patients with hyperlipidemia.<sup>2885</sup> Katayama does not disclose *any* LDL-C related

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20 <sup>2881</sup> Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI<sub>2</sub> and PGI<sub>3</sub> Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

21 <sup>2882</sup> See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

22 <sup>2883</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

23 <sup>2884</sup> Defendants' Joint Invalidity Contentions at 436.

24 <sup>2885</sup> Katayama at 2.

1 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that  
2 reference to provide any such disclosure. The only results disclosed by Katayama were a  
3 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was  
4 administered to patients with borderline-high to high TG levels, and its safety for long term use  
5 in this patient population.<sup>2886</sup> In addition to Katayama’s lack of disclosure regarding LDL-C,  
6 Defendants identify no other basis upon which a person of ordinary skill would have sought to  
7 combine the composition disclosed in Katayama with the Lovaza PDR.

8 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of  
9 administering pure EPA - lowering triglycerides without raising LDL-C.”<sup>2887</sup> However,  
10 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall  
11 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of  
12 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13  
13 were evaluated for improvement in serum triglycerides levels.<sup>2888</sup> It is unclear which of the 26  
14 patients were included in each separate evaluation; therefore one cannot determine the baseline  
15 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack  
16 of a placebo control makes it less likely that the results of this study can be generalized as an  
17 effect on any population as a whole and provides no insight with respect to the very-high TG  
18 patient population.

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22 <sup>2886</sup> *Id.* at 16.

23 <sup>2887</sup> Defendants’ Joint Invalidation Contentions at 436.

24 <sup>2888</sup> Matsuzawa at 7 and 19.

1 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,  
2 and one participant with TG levels > 1,000 mg/dL.<sup>2889</sup> However, when analyzing the lipid  
3 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL  
4 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess  
5 triglyceride levels.”<sup>2890</sup> Fig. 4, which depicts the changes in serum triglycerides, shows that the  
6 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500  
7 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than  
8 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of  
9 undisclosed purity). The identification of three patients with TG levels between 400 and less  
10 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of  
11 ordinary skill would not understand that the reference makes any such disclosure. As discussed  
12 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG  
13 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no  
14 evidence to the contrary.

15 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a  
16 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.<sup>2891</sup> The disclosure  
17 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were  
18 excluded from the LDL-C results because the Friedewald’s Equation was used to calculate LDL-  
19 C levels. The Friedewald’s Equation cannot be used for patients with triglyceride levels of at  
20 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

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22 <sup>2889</sup> *Id.* at 23.

23 <sup>2890</sup> *Id.* at 10.

24 <sup>2891</sup> *Id.* at 11.

1 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of  
2 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary  
3 skill in the art, however, would have expected the same treatment in patients with very high TG  
4 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that  
5 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered  
6 triglyceride levels.<sup>2892</sup> At best, Matsuzawa demonstrates the uncertainty and confusion related to  
7 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify  
8 any other basis upon which a person of ordinary skill would have sought to combine the  
9 composition disclosed in Matsuzawa with the Lovaza PDR.

10 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that  
11 compositions comprising EPA as recited in the asserted claims lowers triglycerides without  
12 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA  
13 increases LDL-C.<sup>2893</sup> Defendants identify no other basis upon which a person of ordinary skill  
14 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank  
15 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the  
16 asserted claims of the '446 patent.

17 (ii) Nozaki and/or Hayashi  
18 Would Not Have Rendered  
19 the Asserted Claims Obvious

20 Defendants contend that the asserted claims of the '446 patent would have been obvious  
21 in view Nozaki and/or Hayashi in combination with other references, but they do not explain

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22 <sup>2892</sup> *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA  
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific  
24 compositions used, or identify the patient populations were observed.

<sup>2893</sup> *See, e.g.,* Rambjor.



1 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
2 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
3 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
4 very high TG patient population.

5 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
6 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
7 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
8 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
9 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
10 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
11 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
12 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
13 patient population were abnormally high and would not have relied upon these results. Further,  
14 the person of skill in the art would not have looked to this patient population to predict the Apo-  
15 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
16 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
17 levels.<sup>2894</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
18 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
19 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
20 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
21 to the very high TG patient population.

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24 <sup>2894</sup> Nozaki at 256.

1 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
2 the EPA and the DHA content in the composition that was administered is unknown. A person  
3 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
4 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
5 C were not statistically significant.<sup>2895</sup> Further, the person of skill in the art would not have  
6 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
7 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
8 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
9 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
10 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
11 administered to the very high TG patient population.

12 Further, Hayashi was a small study conducted in only Japanese patients and was not  
13 placebo controlled. This study would not have been extrapolated to Western populations  
14 because the Japanese diet contains much more fish and has a number of other different attributes.  
15 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
16 populations. In fact, Defendants' own reference states that the results from studies where the  
17 patient population is exclusively Japanese cannot be generalized to other populations.<sup>2896</sup> The  
18 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
19 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
20 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
21 the Japanese respond differently to lipid lowering agents than Westerners.

22 \_\_\_\_\_  
23 <sup>2895</sup> Hayashi at 26, Table I.

24 <sup>2896</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 Further, Defendants have failed to offer a purported combination of references as part of  
2 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
3 motivation to combine Nozaki and Hayashi with the other references of their purported  
4 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
5 references.

6 (iii) Leigh-Firbank and/or Mori  
7 2000 Do Not Disclose  
8 Purported Knowledge that  
9 DHA was Responsible for the  
10 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
11 C levels.”<sup>2897</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
13 rely upon to support this statement does not categorize the increase in LDL-C as a “negative  
14 effect” in light of the overall impact of the disclosed composition on all lipid parameters.  
15 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As  
16 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
17 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—  
18 as in very-high TG patients because patients with higher TG levels had different lipid responses  
19 compared to patients with lower TG levels. Patients with very-high TG levels were considered  
20 fundamentally different from patients with borderline-high or high triglycerides from a lipid  
21 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person  
22 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)

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24 <sup>2897</sup> Defendants’ Joint Invalidity Contentions at 438.

1 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but  
2 would substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was  
4 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,  
5 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride  
6 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either  
7 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A  
8 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any  
9 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the  
10 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)  
11 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated  
12 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA  
13 and DHA.<sup>2898</sup> A person of ordinary skill would understand that studies directed to EPA and  
14 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on  
15 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-  
16 Firbank, because purified EPA and DHA were not administered separately.

17 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent  
18 effects of EPA and DHA individually, even though it administered a combination of EPA and  
19 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions  
20 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet  
21 phospholipid EPA were *independently* associated with the decrease in fasting TGs,<sup>2899</sup> and DHA

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23 <sup>2898</sup> Mori 2006 at 96.

24 <sup>2899</sup> Leigh-Firbank at 440.

1 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state  
2 of the art and numerous publications cited by Defendants.<sup>2900</sup> It is widely accepted that DHA  
3 also has a hypotriglyceridemic effect.

4 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients  
5 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-  
6 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching  
7 away from the claimed invention. “A reference may be said to teach away when a person of  
8 ordinary skill, upon [examining] the reference, would be discouraged from following the path set  
9 out in the reference, or would be led in a direction divergent from the path that was taken by the  
10 applicant.”<sup>2901</sup> Although teaching away is fact-dependent, “in general, a reference will teach  
11 away if it suggests that the line of development flowing from the reference’s disclosures is  
12 unlikely to be productive of the result sought by the applicant.”<sup>2902</sup>

13 Mori 2000 concludes that the changes effected by DHA supplementation “may represent  
14 a more favorable lipid profile than after EPA supplementation.”<sup>2903</sup> For example, it states that  
15 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL  
16 cholesterol and a significant increase in the HDL<sub>2</sub>-cholesterol subfraction, without adverse  
17 effects on fasting glucose concentrations.”<sup>2904</sup> Mori 2000 also states that “[d]espite an increase  
18 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may

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20 <sup>2900</sup> See, e.g. Grimsgaard at 654.

21 <sup>2901</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

22 <sup>2902</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354  
(Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)  
(“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

23 <sup>2903</sup> Mori 2000 at 1092.

24 <sup>2904</sup> Mori 2000 at 1088.

1 be favorable.”<sup>2905</sup> Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori  
2 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the  
3 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away  
4 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for  
5 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,  
6 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration  
7 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,  
8 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
9 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill  
10 would have sought to combine Mori 2000 with the Lovaza PDR.

11 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
12 was known that DHA alone was responsible for the increase in LDL-C levels. Further,  
13 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
14 has little effect on LDL-C levels.<sup>2906</sup> Defendants identify no other basis upon which a person of  
15 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,  
16 Leigh-Firbank and/or Mori 2000.

17 (ii) The ‘446 Patent is not Obvious Over the  
18 Omacor PDR/Lovaza PDR, in Combination  
19 with Katayama and/or Matsuzawa, and/or  
20 Takaku, Further in View of Nozaki and/or  
21

22 \_\_\_\_\_  
23 <sup>2905</sup> Mori 2000 at 1092.

24 <sup>2906</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '446 Patent, Defendants present a combination of nine references:

“the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki.”<sup>2907</sup>

Defendants also present charts purporting to assert that an additional 58 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 58 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>2908</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>2909</sup> Defendants’ contentions are no more than an assertion that certain

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<sup>2907</sup> Defendants’ Joint Invalidity Contentions at 435.

<sup>2908</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2909</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 claim elements were known in the prior art. Throughout their contentions, Defendants’  
2 selectively cite to data points in a reference without considering other disclosures or even the  
3 reference as a whole. Each reference, however, must be evaluated for all that it teaches.<sup>2910</sup>  
4 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method  
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the  
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR  
8 further do not disclose a method to effect the claimed TG reduction without substantially  
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA  
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the  
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose  
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375  
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500  
14 mg/dL) TG levels. The proposed combinations do not render the independent claim of the ’446  
15 Patent obvious and Defendants’ burden to prove otherwise is especially difficult because the  
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both  
17 generally and the Lovaza package insert specifically) during prosecution.<sup>2911</sup>

18 The analysis of the independent claim of the ’446 Patent is incorporated into all asserted  
19 claims that depend from this Claim.

20 (a) A Person of Ordinary Skill Would  
21 Not Have Been Motivated to

22 <sup>2910</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2911</sup> *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).



3 For an invention to be obvious, there must have been an “apparent reason” to make it.  
4 The subject matter of the ‘446 patent claims would not have been obvious in light of these  
5 references because a person of ordinary skill would not have been motivated to purify EPA or  
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
7 levels without an increase in LDL-C levels.

8 (i) Grimsgaard, Katayama,  
9 Matsuzawa and/or Takaku  
10 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

11 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the  
12 “known clinical benefits of administering pure EPA - lowering triglycerides without raising  
13 LDL-C.” As discussed in Section V.F.3.c.1.a.i.a.i, incorporated herein by reference, Katayama  
14 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to  
15 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported  
16 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that  
17 the LDL-C results obtained were a clinical benefit.

18 Defendants also rely on Grimsgaard to support their assertion that “administration of  
19 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”<sup>2912</sup> However,  
20 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on  
21 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

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23 \_\_\_\_\_  
<sup>2912</sup> Defendants’ Joint Invalidity Contentions at 438-39.

1 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA  
2 administered to people with normal triglyceride levels for 7 weeks.<sup>2913</sup> The results from the  
3 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the  
4 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that  
5 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid  
6 supplements, which is consistent with previous studies which “suggested that serum HDL-C is  
7 better maintained with oil rich in DHA than oil rich in EPA.”<sup>2914</sup> Although Grimsgaard states  
8 that EPA may produce a small decrease in serum total cholesterol, it does not specifically  
9 comment on EPA’s effect on LDL-C.

10 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to  
11 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in  
12 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-  
13 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”<sup>2915</sup> The  
14 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the  
15 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s  
16 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to  
17 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s  
18 disclosure highlights the importance of a placebo-controlled study and why results compared  
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22 <sup>2913</sup> Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG  
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG  
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

<sup>2914</sup> Grimsgaard at 654.

<sup>2915</sup> Defendants’ Joint Invalidation Contentions at 428 n.73.

only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

TABLE 4  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>2</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>2</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>2</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>2</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>2-5</sup> One-sample t test of difference between baseline and 7 wk: <sup>3</sup> P < 0.001, <sup>4</sup> P < 0.01, <sup>5</sup> P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”<sup>2916</sup> However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements.”<sup>2917</sup> Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that

<sup>2916</sup> Grimsgaard at 657.

<sup>2917</sup> Grimsgaard at 654.

1 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did  
2 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and  
3 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and  
4 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified  
5 DHA results in increased LDL-C levels while administration of purified EPA resulted in a  
6 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did  
7 not have statistically significantly effects on LDL-C compared to placebo.<sup>2918</sup> A person of  
8 ordinary skill would not draw conclusions regarding differences between EPA and DHA based  
9 on statistically insignificant results.

10 Defendants also rely on Takaku to support their assertion that “clinical benefits of  
11 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the  
12 art.<sup>2919</sup> Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and  
13 safety of Epadel (of undisclosed purity)<sup>2920</sup> based on long-term administration.<sup>2921</sup>

14 A person of ordinary skill would not have concluded based on Takaku that EPA lowers  
15 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly  
16 acknowledges that “only a few subjects were examined” and cautions against drawing a  
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18 <sup>2918</sup>In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a  
19 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to  
20 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have  
21 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make  
22 such arguments for the obvious reason that it does not support their argument that EPA was known to have little or  
23 no impact on LDL-C levels.

21 <sup>2919</sup> Defendants’ Joint Invalidity Contentions at 436.

22 <sup>2920</sup> It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by  
23 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),  
24 Nakamura at 23 (Epadel with purity > 90%).

<sup>2921</sup> Takaku at ICOSAPENT\_DFNDT00006834.

1 conclusion “only from the results of the present study.”<sup>2922</sup> Because the study did not include  
2 any placebo control, a person of ordinary skill in the art would understand these reports do not  
3 provide the ability to conclude that the observed lipid effects would have occurred independent  
4 of the drug that is administered. In addition, the study was conducted exclusively in Japanese  
5 patients, and a person of ordinary skill would not have expected the results to be applicable to the  
6 general population.<sup>2923</sup>

7 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a  
8 person of ordinary skill would not have expected the results to be applicable to patients with  
9 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because  
10 measurement was not feasible due to “insufficient sample.”<sup>2924</sup> It is possible that patients with  
11 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in  
12 calculating LDL-C levels when triglyceride level is above 400 mg/dL.<sup>2925</sup> Moreover, the study  
13 does not provide different LDL-C graphs based on the baseline triglyceride levels.<sup>2926</sup> Therefore,  
14 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had  
15 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C  
16 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile  
17 throughout the study period, decreasing slightly at times but increasing by more than 8% at other  
18  
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20 <sup>2922</sup> Takaku at ICOSAPENT\_DFNDT00006897.

21 <sup>2923</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.”)

22 <sup>2924</sup> Takaku at ICOSAPENT\_DFNDT00006884.

23 <sup>2925</sup> See Matsuzawa at ICOSPENT\_DFNDTS00006450.

24 <sup>2926</sup> Takaku at Fig. 13, ICOSAPENT\_DFNDT00006882.

1 times.<sup>2927</sup> Because of this volatility, a person of ordinary skill would not be able to conclude  
2 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in  
3 LDL-C, stating only that the fluctuation in LDL-C was not significant.<sup>2928</sup>

4 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA  
5 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has  
6 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the  
7 administration of *fish oil* to hypercholesterolemia patients.”<sup>2929</sup> In contrast, Takaku states merely  
8 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary  
9 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study  
10 was attributable to fish oil in general, not EPA specifically.

11 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate  
12 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other  
13 studies cited by Defendants suggest that EPA increases LDL-C.<sup>2930</sup> Defendants identify no other  
14 basis upon which a person of ordinary skill would have sought to combine the Omacor  
15 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

16 (ii) Nozaki and/or Hayashi  
17 Would Not Have Rendered  
18 the Asserted Claims Obvious

18 Defendants contend that the asserted claims of the ’446 patent would have been obvious  
19 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
20 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

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22 <sup>2927</sup> Takaku at Fig. 14, ICOSAPENT\_DFNDT00006883.

23 <sup>2928</sup> Takaku at ICOSAPENT\_DFNDT00006897.

24 <sup>2929</sup> Takaku at ICOSAPENT\_DFNDT00006897.

<sup>2930</sup> See, e.g., Rambjor.

1 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
2 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
3 very high TG patient population.

4 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
5 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
6 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
7 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
8 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
9 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
10 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
11 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
12 patient population were abnormally high and would not have relied upon these results. Further,  
13 the person of skill in the art would not have looked to this patient population to predict the Apo-  
14 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
15 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
16 levels.<sup>2931</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
17 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
18 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
19 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
20 to the very high TG patient population.

21 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
22 the EPA and the DHA content in the composition that was administered is unknown. A person  
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24 <sup>2931</sup> Nozaki at 256.

1 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
2 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
3 C were not statistically significant.<sup>2932</sup> Further, the person of skill in the art would not have  
4 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
5 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
6 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
7 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
8 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
9 administered to the very high TG patient population.

10 Further, Hayashi was a small study conducted in only Japanese patients and was not  
11 placebo controlled. This study would not have been extrapolated to Western populations  
12 because the Japanese diet contains much more fish and has a number of other different attributes.  
13 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
14 populations. In fact, Defendants' own reference states that the results from studies where the  
15 patient population is exclusively Japanese cannot be generalized to other populations.<sup>2933</sup> The  
16 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
17 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
18 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
19 the Japanese respond differently to lipid lowering agents than Westerners.

20 Further, Defendants have failed to offer a purported combination of references as part of  
21 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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23 <sup>2932</sup> Hayashi at 26, Table I.

24 <sup>2933</sup> Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).



1 motivation to combine Nozaki and Hayashi with the other references of their purported  
2 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
3 references.

4 (iii) Grimsgaard, Mori 2000  
5 and/or Maki Do Not Disclose  
6 Purported Knowledge that  
7 DHA was Responsible for the  
8 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
11 C levels.”<sup>2934</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
13 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”  
14 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
15 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.  
16 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
17 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or  
18 Maki—as in very-high TG patients because patients with higher TG levels had different lipid  
19 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
20 considered fundamentally different from patients with borderline-high or high triglycerides from  
21 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of  
22 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

23 \_\_\_\_\_  
24 <sup>2934</sup> Defendants’ Joint Invalidity Contentions at 438.

1 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would  
2 substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known  
4 that “DHA was responsible for the increase in LDL-C levels.”<sup>2935</sup> The discussion related to  
5 Grimsgaard in Section V.F.3.c.1.a.ii.a.i and Mori 2000 in Section V.F.3.c.1.a.i.a.iii is  
6 incorporated herein by reference.

7 Defendants argue that Maki discloses the administration of purified DHA resulted in the  
8 desired reduction of TGs, but also significantly increased LDL-C levels.<sup>2936</sup> Maki was designed  
9 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with  
10 below-average levels of HDL-C levels.<sup>2937</sup> The DHA supplemented group was administered  
11 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,  
12 monounsaturated and polyunsaturated fatty acids.<sup>2938</sup> Therefore, Maki demonstrated that when  
13 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average  
14 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is  
15 observed.<sup>2939</sup> However, one cannot attribute the rise in LDL-C solely to DHA, because the  
16 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have  
17 also contributed to the elevation in LDL cholesterol.”<sup>2940</sup> Further, Maki admits that the  
18

19 \_\_\_\_\_  
<sup>2935</sup> Defendants’ Joint Invalidation Contentions at 438-39.

20 <sup>2936</sup> Defendants’ Joint Invalidation Contentions at 438.

21 <sup>2937</sup> Maki at 190.

22 <sup>2938</sup> Maki at 191.

23 <sup>2939</sup> Maki at 195.

24 <sup>2940</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

1 “mechanism(s) responsible for the changes in the lipid profile associated with DHA  
2 supplementation are not fully understood.”<sup>2941</sup> Therefore, the results of Maki are inconclusive as  
3 to DHA’s effect alone on LDL-C levels.

4 Defendants mischaracterize the rise in LDL-C associated with the administration of  
5 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-  
6 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in  
7 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol  
8 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of  
9 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level  
10 less worrisome.”<sup>2942</sup> Therefore, when one of ordinary skill in the art reviewed all the lipid effects  
11 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was  
12 “less worrisome” because of the “potentially favorable effects on triglycerides, the  
13 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense  
14 particles.”<sup>2943</sup>

15 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
16 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
17 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
18 has little effect on LDL-C levels.<sup>2944</sup> Defendants identify no other basis upon which a person of  
19 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,  
20 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

21 \_\_\_\_\_  
22 <sup>2941</sup> Maki at 197.

23 <sup>2942</sup> Maki at 197.

24 <sup>2943</sup> Maki at 197.

<sup>2944</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 (iii) The '446 Patent is not Obvious Over the  
2 Omacor PDR/Lovaza PDR, in Combination  
3 with Katayama in View of Satoh and/or in  
4 View of Satoh or Shinozaki in Further View  
5 of Contacos

6 With respect to the '446 Patent, Defendants present a combination of five references: “the  
7 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering  
8 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in  
9 further view of Contacos.”<sup>2945</sup> Defendants also present charts purporting to assert that an  
10 additional 60 references may be combined in order to render the Claims obvious. Not only do  
11 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate  
12 references, they additionally do not suggest any identify for combining these references.  
13 Although Defendants need not point to an explicit statement in the prior art motivating the  
14 combination of these references, any assertion of an “apparent reason” to combine must find a  
15 basis in the factual record.<sup>2946</sup> Defendants’ unsupported cobbling of selective disclosures  
16 represents hindsight reconstruction.<sup>2947</sup> Defendants’ contentions are no more than an assertion

17 <sup>2945</sup> Defendants’ Joint Invalidity Contentions at 436.

18 <sup>2946</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
19 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
20 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
21 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi  
22 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
23 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
24 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>2947</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that certain claim elements were known in the prior art. Throughout their contentions,  
2 Defendants' selectively cite to data points in a reference without considering other disclosures or  
3 even the reference as a whole. Each reference, however, must be evaluated for all that it  
4 teaches.<sup>2948</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
5 obviousness.

6 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
7 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty  
8 acid compositions or administration period. The Lovaza PDR further does not disclose a method  
9 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza  
10 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference  
11 would cause a significant increase in LDL-C levels in the very high TG patient population, for  
12 whom the product is indicated. At most, the Lovaza PDR discloses administration of a  
13 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an  
14 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG  
15 levels.

16 Defendants formulate an obviousness argument that relies on Contacos.<sup>2949</sup> However,  
17 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim  
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23 <sup>2948</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>2949</sup> *Id.*

1 element, an “apparent reason” or motivation to combine the elements in the manner claimed,<sup>2950</sup>  
2 or “a reasonable expectation of success”<sup>2951</sup> of achieving the claimed invention.

3 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and  
4 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,  
5 Contacos fails to provide motivation to administer purified EPA to a very high TG patient  
6 population and does not provide any reasonable expectation of success in lowering TG levels in  
7 the very high TG patient population without increasing LDL-C. Contacos also fails to provide  
8 motivation to administer purified EPA to a very high TG patient population and does not provide  
9 any reasonable expectation of success in lowering TG levels in the very high TG patient  
10 population without increasing LDL-C.

11 The proposed combinations do not render the independent claim of the ’446 Patent  
12 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
13 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally  
14 and the Lovaza package insert specifically) during prosecution.<sup>2952</sup>

15 The analysis of the independent claim of the ’446 Patent is incorporated into all asserted  
16 claims that depend from this Claim.

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18 <sup>2950</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
19 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
20 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 <sup>2951</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

23 <sup>2952</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 (a) A Person of Ordinary Skill Would  
2 Not Have Been Motivated to  
3 Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with EPA of  
4 the Recited Composition

5 For an invention to be obvious, there must have been an “apparent reason” to make it.  
6 The subject matter of the ‘446 patent claims would not have been obvious in light of these  
7 references because a person of ordinary skill would not have been motivated to purify EPA or  
8 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
9 levels without an increase in LDL-C levels.

10 (i) Katayama, Satoh and/or  
11 Shinozaki Do Not Disclose  
12 Purported Known Clinical  
Benefits of Administering  
Pure EPA

13 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical  
14 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As  
15 discussed in Section V.F.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely  
16 confirms the safety of long term treatment of Epadel and its ability to lower both serum total  
17 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone  
18 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or  
19 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary  
20 skill view these references as teaching such a benefit for very-high TG patients.

21 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
22 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
23 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when  
24

1 compared to baseline, there was no significant effect when compared to placebo.<sup>2953</sup>  
2 Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing  
3 LDL-C to be a "clinical benefit" is incorrect.<sup>2954</sup> Satoh does not disclose or suggest that the  
4 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these  
5 references as teaching such a benefit for very-high TG patients. As discussed above, one of  
6 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500  
7 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,  
8 however, would have expected that fish oils (and other TG lowering agents) would substantially  
9 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to  
10 administer purified EPA to a very high TG patient population and does not provide any  
11 reasonable expectation of success in lowering TG levels in the very high TG patient population  
12 without increasing LDL-C.

13 Further, Satoh was a small study conducted in only Japanese patients. This study would  
14 not have been extrapolated to Western populations because the Japanese diet contains much  
15 more fish and has a number of other different attributes. The Japanese consume a higher amount  
16 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference  
17 states that the results from studies where the patient population is exclusively Japanese cannot be  
18 generalized to other populations.<sup>2955</sup> The Japanese diet comprises between 8 and 15 times more  
19 EPA and DHA than typical the typical Western diet. The Western diet typically consists of  
20 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a

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22 <sup>2953</sup> Satoh at 145.

23 <sup>2954</sup> Defendants' Joint Invalidation Contentions at 436.

24 <sup>2955</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").



1 person of ordinary skill would understand that the Japanese respond differently to lipid lowering  
2 agents than Westerners.

3 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))  
4 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.  
5 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without  
6 increasing LDL-C to be a "clinical benefit" is incorrect.<sup>2956</sup> Shinozaki says nothing about an  
7 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by  
8 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."<sup>2957</sup> In  
9 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis  
10 upon which a person of ordinary skill would have sought to combine the composition disclosed  
11 in Shinozaki.

12 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion  
13 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by  
14 Defendants suggest that EPA increases LDL-C.<sup>2958</sup> Defendants identify no other basis upon  
15 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,  
16 Satoh, Shinozaki and/or Contacos.

17 (ii) Geppert and/or Kelley Do  
18 Not Disclose Purported  
19 Knowledge that DHA was  
20  
21

22 <sup>2956</sup> Defendants' Joint Invalidation Contentions at 436.

23 <sup>2957</sup> Shinozaki at 107-109.

24 <sup>2958</sup> See, e.g., Rambjor.

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2  
3 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
4 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
5 C levels.”<sup>2959</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
6 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
7 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”  
8 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
9 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,  
10 respectively. As discussed above in Section III, a person of ordinary skill would not expect the  
11 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or  
12 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid  
13 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
14 considered fundamentally different from patients with borderline-high or high triglycerides from  
15 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a  
16 person of ordinary skill in the art would have expected that fish oils (and other TG lowering  
17 agents) would not increase LDL-C substantially in patients with normal to borderline high TG  
18 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in  
19 patients with very high TG levels.

20 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA  
21 was responsible for the increase in LDL-C levels.”<sup>2960</sup> Both Geppert and Kelley administer  
22 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.

23 <sup>2959</sup> Defendants’ Joint Invalidity Contentions at 438.

24 <sup>2960</sup> Defendants’ Joint Invalidity Contentions at 436.

1 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the  
2 independent effects of DHA because it is not clear how much of the supplement's effects can be  
3 attributed to DHA.<sup>2961</sup> For example, Defendants' own prior art teaches that changes in fatty acid  
4 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.<sup>2962</sup>

5 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to  
6 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been  
7 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior  
8 studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."<sup>2963</sup> Rather than reading  
9 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior  
10 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there  
11 was confusion in the art and it was unclear whether DHA increased LDL-C.

12 A person of ordinary skill would have expected that Geppert's results would be  
13 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA  
14 was the only component of fish oil to increase LDL-C. For example, there is no data comparing  
15 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying  
16 explain the mechanism of LDL-C increase.<sup>2964</sup> A person of ordinary skill would have not  
17 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

18 Defendants contend that Kelley shows that DHA was responsible for the increase in  
19 LDL-C.<sup>2965</sup> In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day  
20

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21 <sup>2961</sup> See Mori 2006 at 96.

22 <sup>2962</sup> Maki at 197.

23 <sup>2963</sup> Geppert at 784.

24 <sup>2964</sup> *Id.*

<sup>2965</sup> Defendants' Joint Invalidation Contentions at 436.

1 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible  
2 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon  
3 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate  
4 therapy.<sup>2966</sup> Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in  
5 context with the other lipid effects reported in the study. Kelley states that:

6 DHA supplementation may lower the risk of CVD by reducing  
7 plasma triacylglycerols; triacylglycerol:HDL; the number of  
8 small, dense LDL particles; and mean diameter of VLDL particles.  
9 An increase was observed in fasting LDL cholesterol, but it  
10 is unlikely this increase is detrimental because no increase was  
11 observed in the overall number of LDL particles; actually, there  
12 was an 11% reduction that was statistically not significant. The  
13 reason LDL cholesterol increased despite no change in LDL  
14 particle number was that the LDL particles were made larger and  
15 hence more cholesterol rich by DHA treatment.<sup>2967</sup>

16 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation  
17 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle  
18 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
19 concentrations of atherogenic lipids and lipoproteins and increased concentrations of  
20 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular  
21 health.”<sup>2968</sup> Rather than concluding that DHA was uniquely responsible for a rise in LDL-C  
22 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely  
23 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with  
24 negative attributes, a person of ordinary skill would understand that the reference taught towards  
the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400

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<sup>2966</sup> Kelley at 329.

<sup>2967</sup> Kelley at 329

<sup>2968</sup> Kelley at 324, 332.

1 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the  
2 very high TG patient population to be different in terms of their response to lipid therapy,  
3 including administration of DHA. A person of ordinary skill in the art would have expected that  
4 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with  
5 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a  
6 substantial increase in LDL-C in patients with very high TG levels.

7 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was  
8 known that DHA was responsible for the increase in LDL-C levels.

9 Throughout their contentions, Defendants' selectively cite to data points in a reference  
10 without considering other disclosures or even the reference as a whole. Each reference,  
11 however, must be evaluated for all that it teaches.<sup>2969</sup> As is the case with Kelley, Defendants use  
12 hindsight to characterize a reference based on LDL-C levels alone without considering the other  
13 lipid effects studied, considered and reported.<sup>2970</sup> The isolated manner in which Defendants  
14 select such data points is not the approach that a person of ordinary skill would have taken at the  
15 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.  
16 A person of ordinary skill would take into consideration the entire disclosure of a reference,  
17 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,  
18 without explanation, the other effects of DHA that a person of ordinary skill would consider.  
19 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a  
20 favorable effect in hypertriglyceridemic patients.

21  
22 <sup>2969</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>2970</sup> Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation  
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean  
diameters of these particles in fasting and postprandial plasma.").



1 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG  
 2 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an  
 3 LDL-C lowering medication such as a statin.<sup>2973</sup> However, the risk of rhabdomyolysis increased  
 4 five-fold if fibrates were administered with a statin.<sup>2974</sup> Therefore, physicians were reluctant to  
 5 recommend, and patients were hesitant embrace, a combination fibrate/statin course of  
 6 treatment.<sup>2975</sup> Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to  
 7 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,  
 8 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

9 In any event, a person of ordinary skill in the art would have understood that omega 3-  
 10 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high  
 11 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would  
 12 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs  
 13 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2976</sup>	-20%	+45%
Lovaza/Omacor <sup>2977</sup>	-6%	+45%

14  
 15  
 16  
 17  
 18 That Epadel has been approved for decades but not approved for use in the very high TG  
 19 patient population prior to the invention of the asserted patents is a real-world reflection of the

20 <sup>2973</sup> Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate  
 21 is often required to achieve LDL-C and non-HDL-C goals”);

22 <sup>2974</sup> See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with  
 23 statins.”).

24 <sup>2975</sup> See *Id.*, ¶ 17

<sup>2976</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

<sup>2977</sup> Chan 2002 I at 2381 (Table 3).

1 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
2 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
3 been countless studies conducted which administer Epadel and report the effects observed.  
4 Although a few studies administer Epadel to a patient population which included a few patients  
5 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
6 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

7 Defendants offer no “apparent reason” to administer EPA as claimed to patients with  
8 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on  
9 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients  
10 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”<sup>2978</sup>

11 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500  
12 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG  
13 reduction and the increased conversion of VLDL to LDL particles.<sup>2979</sup>

14 It was well known at the time of the invention that omega-3 fatty acids, including both  
15 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant  
16 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3  
17 fatty acids worked in part by inhibiting VLDL production and improving the conversion of  
18 VLDL particles to LDL.<sup>2980</sup> A person of ordinary skill in the art understood that EPA and DHA

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20 <sup>2978</sup> Defendants’ Joint Invalidity Contentions at 437.

21 <sup>2979</sup> See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese  
22 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and  
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in  
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

23 <sup>2980</sup> Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced  
24 decrease in VLDLs after n-3 fatty acid treatment”)



1 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when  
2 discussing the TG-lowering mechanism of omega-3 fatty acids.<sup>2981</sup> The discussion related to the  
3 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and  
4 incorporated herein by reference.

5 In fact, it was well understood that the degree of LDL-C elevation observed with  
6 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG  
7 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels  
8 the most in patients with the highest pretreatment TG levels.<sup>2982</sup> Therefore, a person of ordinary  
9 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct  
10 consequence of lowering triglycerides in patients with TG levels  $\geq 500$  mg/dL. The rise in LDL-  
11 C was often offset by concurrent treatment with statins.<sup>2983</sup> The safety and efficacy of using  
12 prescription omega-3 in combination with a statin has been well-established.<sup>2984</sup>

13 Although an increase in LDL-C was generally observed when omega-3 fatty acids were  
14 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a  
15 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.  
16 Therefore, the final LDL-C concentration may still be in the normal range.<sup>2985</sup> Furthermore, it  
17 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>2986</sup>

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19 <sup>2981</sup> Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*  
20 *Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

21 <sup>2982</sup> See Bays 2008 Rx Omega-3 p. 402.

22 <sup>2983</sup> See Harris 2008 at 14, McKenney at 722.

23 <sup>2984</sup> McKenney at 722-23.

24 <sup>2985</sup> See Westphal at 918, Harris 1997 at 389.

<sup>2986</sup> See Pownall at 295 (stating that “[t]reatment with  $\omega$ -3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesteryl ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he

1 In two pivotal studies in very-high TG patients, both of which used prospective,  
2 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL  
3 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).<sup>2987</sup> Correspondingly, prescription  
4 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.<sup>2988</sup> Therefore,  
5 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can  
6 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net  
7 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in  
8 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also  
9 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the  
10 number of small, dense LDL particles to larger LDL particles.<sup>2989</sup> Lovaza/Omacor “adversely  
11 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration  
12 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”<sup>2990</sup>  
13 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3  
14 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not

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18 increase in LDL, which was substantial on a percentage basis, has been a common finding in [very-  
19 high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the  
20 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute  
21 pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this  
22 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty  
23 acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in  
24 LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by  
decreased non-HDL-C levels (TC minus HDL-C”).

<sup>2987</sup> McKenney 2007 at 721 (citing Harris 1997 and Pownall).

<sup>2988</sup> McKenney 2007 at 722 (see Fig. 1).

<sup>2989</sup> McKenney 2007 at 722 (citing Calabresi and Stalenhoef).

<sup>2990</sup> Stalenhoef at 134.

1 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention  
2 of [coronary heart disease].”<sup>2991</sup>

3           Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at  
4 the time of the claimed inventions would have been motivated to find a therapy that would  
5 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting  
6 LDL-C levels,”<sup>2992</sup> one of ordinary skill in the art at the time of the invention understood that the  
7 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with  
8 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to  
9 increase in very-high TG patients, and in some instances the rise was not concerning because  
10 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final  
11 concentration would still be in the normal range. When LDL-C levels increased beyond what  
12 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively  
13 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of  
14 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to  
15 identify any other basis upon which a person of ordinary skill would have been motivated to find  
16 a therapy that would reduce TG levels in patients with very-high TG levels without negatively  
17 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood  
18 that EPA therapy would *not* reduce Apo-B<sup>2993</sup> (which is a reflection of total atherogenic  
19 lipoproteins)<sup>2994</sup> in very high TG patients, and accordingly would not have been motivated to  
20 administer the claimed EPA composition to the very high TG patient population.

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22 <sup>2991</sup> Harris 1997 at 389.

23 <sup>2992</sup> Defendants’ Joint Invalidity Contentions at 437.

24 <sup>2993</sup> *see* Section V.O.

<sup>2994</sup> *see* Section III.

1 Defendants make the conclusory allegation that “routine optimization” by a person of  
2 ordinary skill would yield the claimed invention. Defendants, however, have offered no  
3 explanation to support that allegation and they further fail to establish any of the required criteria  
4 of “routine optimization” or the prerequisites to this argument. They also fail to provide any  
5 factual detail to support their allegation and they fail to link the allegation to any particular claim  
6 or claim element. Defendants mere allegation constitute an improper placeholder to later  
7 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,  
8 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the  
9 combinations alleged by Defendants and, for the same reasons, it would not be routine to  
10 combine such references. Where, for example, defendants argue that it would be routine to go  
11 from the high TG patient population to the very high TG patient population, they provide no  
12 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill  
13 would have understood these patient populations to be distinct with different impacts of lipid  
14 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would  
15 not have considered the dosage modification suggested by defendants to be routine; Defendants’  
16 argument to the contrary represents hindsight bias.

17 In addition, a person of ordinary skill would have no motivation to combine these  
18 references because EPA would have been expected to have same result as the mixture of EPA  
19 and DHA used in Lovaza/Omacor.

20 (v) A Person of Ordinary Skill Would Not Have  
21 Had a Reasonable Expectation of Success  
22 with the Combinations Defendants  
Hypothesize

23 Defendants provide no evidence that a person or ordinary skill would have had a  
24 reasonable expectation of successfully obtaining the claimed invention—a method of reducing

1 triglycerides in a subject having very-high triglyceride levels by administering EPA of the  
 2 recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by  
 3 combining the references cited by defendants. For a particular combination of references, there  
 4 must be a reasonable expectation that the combination will produce the claimed invention. In  
 5 this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with  
 6 very-high TG levels.<sup>2995</sup> A person of ordinary skill would have expected EPA, like  
 7 Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG  
 8 patient population. As discussed in Section III and above, it was well known that TG-lowering  
 9 agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for  
 10 normal to high TG patients, but caused significant increases in LDL-C levels for patients with  
 11 very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary  
 12 skill to expect anything to the contrary. A person of ordinary skill would have understood that  
 13 omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among  
 14 very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>2996</sup>	-20%	+45%
Lovaza/Omacor <sup>2997</sup>	-6%	+45%

20 <sup>2995</sup> As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to  
 21 have the same TG lowering mechanism and would have further understood that the increase in LDL-C  
 22 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of  
 ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar  
 fashion to Lovaza or DHA alone.

23 <sup>2996</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

24 <sup>2997</sup> Chan 2002 I at 2381 (Table 3).

1           Accordingly, a person of ordinary skill would *not* have a reasonable expectation of  
2 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients  
3 with very-high TG levels.<sup>2998</sup>

4           Defendants’ position that a person of ordinary skill would have had a reasonable  
5 expectation of success in administering purified EPA to patients with very high triglyceride  
6 levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that  
7 Defendants’ provide no evidence that anyone thought to administer Epadel.<sup>2999</sup> Epadel was  
8 available for many years prior to the invention of the ’446 patent, to patients with very-high TGs  
9 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,  
10 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of  
11 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by  
12 Defendants are directed to the use of purified EPA in the very-high TG population.

13           Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
14 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
15 countless studies conducted which administer Epadel and report the effects observed. Although  
16 a few studies administer Epadel to a patient population which included a few patients with TG  
17 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
18 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
19 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
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23 <sup>2998</sup> Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall  
effect on lipid parameters, teaching away from this combination.

24 <sup>2999</sup> Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not  
examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
2 triglycerides.

3 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients  
4 with borderline-high/high TG, it would have been obvious to try administering purified ethyl  
5 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants  
6 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of  
7 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.<sup>3000</sup>  
8 Defendants' contentions are no more than a demonstration that certain claim elements was  
9 known in the prior art and demonstrates impermissible hindsight reconstruction.<sup>3001</sup> As is  
10 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,  
11 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA  
12 and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that  
13 administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,  
14 none of these references would provide a person of ordinary skill in the art with a reasonable  
15 expectation of successfully obtaining the claimed invention even if there were reasons to  
16 combine disparate, independent elements found in the prior art, which there were not.

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<sup>3000</sup> Defendants' Joint Invalidity Contentions at 439-40.

23 <sup>3001</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
24 KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.").

**TABLE 4**  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>3</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>3</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>3</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>3</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>3</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>3</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>4</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>3</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>3-5</sup> One-sample *t* test of difference between baseline and 7 wk: <sup>3</sup>  $P < 0.001$ , <sup>4</sup>  $P < 0.01$ , <sup>5</sup>  $P < 0.05$ .

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.

To the extent that Defendants' arguments are based on results that are not statistically significant and not reported by Grimsgaard as significant, a person of ordinary skill would not draw conclusions from these statistically insignificant differences. Indeed, the standard deviation for the changes reported is greater than the value of the change itself.

Defendants argue that it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. However, the



1 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-  
2 try” proves that the claimed invention was obvious where the prior art did not suggest what to  
3 try.<sup>3002</sup> Rather than there being a limited number of options, the state of the art provided a  
4 plethora of compositions and administration protocols associated with multiple kinds of TG-  
5 lowering therapies.<sup>3003</sup> There were not a finite number of options for a person of ordinary skill  
6 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient  
7 population.

8 Defendants argue that a person of ordinary skill at the time of the invention, based on  
9 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone  
10 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to  
11 no impact on LDL-C levels.<sup>3004</sup> However, that statement does not conform with what was  
12 known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high  
13 TG patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor  
14 were both known to have little or no effect on LDL-C in patients with borderline-high/high TG  
15 levels.

16 With the lack of any reasonable expectation of success, Defendants argue that their  
17 proposed combination amounts to a simple substitution of one known element for another, and  
18 that that these changes yield predictable results.<sup>3005</sup> Such an argument, however, represents pure  
19 and impermissible hindsight bias and further does not consider that reasons for which a person of  
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22 <sup>3002</sup> See *Sanofi*, 748 F.3d at 1360–61.

23 <sup>3003</sup> See *supra* Section III.

24 <sup>3004</sup> Defendants’ Joint Invalidation Contentions at 439.

<sup>3005</sup> Defendants’ Joint Invalidation Contentions at 440.

1 ordinary skill would not be motivated to combine these references and affirmatives ways in  
2 which the art taught away from these combinations.

3 (b) Defendants Have Not Shown It Would Have Been  
4 Obvious to Administer Purified EPA in the Dosing  
Regimen Recited in the Claims

5 (i) The '446 Patent is not Obvious Over WO  
6 '118 or WO '900, in Combination with the  
Lovaza PDR, and Further in View of Leigh-  
7 Firbank and/or Mori 2000

8 With respect to the '446 Patent, Defendants present a combination of five references:  
9 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the  
10 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."<sup>3006</sup> Defendants also  
11 present charts arguing that an additional 61 references may be combined in order to render the  
12 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill  
13 would combine 61 separate references, they additionally do not identify any motivation for  
14 combining these references.<sup>3007, 3008</sup> Although Defendants need not point to an explicit statement  
15 in the prior art motivating the combination of these references, any assertion of an "apparent

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<sup>3006</sup> Defendants' Joint Invalidity Contentions at 442.

17 <sup>3007</sup> Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in  
18 V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama,  
19 Matsuzawa, Matakai, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki,  
20 Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-  
Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a person of  
ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor" similarly fails to meet the  
disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these  
references. *See* Defendants' Joint Invalidity Contentions at 442.

21 <sup>3008</sup> Defendants' bare assertion that "the motivation or reason to combine or modify the prior art to create  
22 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,"  
and that "[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person  
23 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
or modifying references to render obvious the claimed inventions of the asserted claims," fails to meet the disclosure  
requirements of the Nevada Local Patent Rules. *See* Defendants' Joint Invalidity Contentions at 433-34.

1 reason” to combine must find a basis in the factual record.<sup>3009</sup> Defendants’ unsupported cobbling  
2 of selective disclosures represents hindsight reconstruction.<sup>3010</sup> Defendants’ contentions are no  
3 more than an assertion that certain claim elements were known in the prior art. Throughout their  
4 contentions, Defendants’ selectively cite to data points in a reference without considering other  
5 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
6 that it teaches.<sup>3011</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
7 obviousness.

8 WO ‘118 is directed at the composition containing EPA for the purpose of preventing the  
9 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO ‘118  
10 is directed, “in particular, [to] preventing occurrence of cardiovascular events in  
11 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the  
12 risk of the cardiovascular events.”<sup>3012</sup> Contrary to Defendants’ assertion that WO ‘118 discloses  
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15 <sup>3009</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
16 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
17 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
18 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
19 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point  
20 “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation  
21 to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties  
22 and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.  
23 Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*  
24 *facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and  
concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art  
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

21 <sup>3010</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
22 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 <sup>3011</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>3012</sup> WO ‘118 at 9.

1 “the administration of 4 g of pure EPA with no DHA,”<sup>3013</sup> WO ’118 fails to disclose the claimed  
2 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive  
3 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified  
4 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction  
5 without substantially increasing LDL-C. WO ’118 discloses a composition with a wide range of  
6 possible EPA content, dosages, and teaches that DHA is a “preferable fatty acid” to include in  
7 the disclosed composition.<sup>3014</sup>

8 WO ’118 does not disclose administration of highly-purified ethyl-EPA to the target  
9 population of the claimed invention. The asserted claims are directed to persons with severe  
10 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO ’118 on the other hand only  
11 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.<sup>3015</sup> WO  
12 ’118’s emphasis on reducing cardiovascular events suggests that its disclosure is directed to  
13 patients with borderline-high to high TG levels, since the primary goal for patients with very-  
14 high TG is to prevent acute pancreatitis by decreasing TG levels.<sup>3016</sup>

15 WO ’118 also does not distinguish EPA from DHA in its disclosures regarding the  
16 effectiveness of the substances for treating hypertriglyceridemia.<sup>3017</sup> WO ’118 states that  
17 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-  
18 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +  
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20 <sup>3013</sup> Defendants’ Joint Invalidity Contentions at 442.

21 <sup>3014</sup> WO ’118 at 22-23.

22 <sup>3015</sup> WO ’118 at 8.

23 <sup>3016</sup> See Section III.

24 <sup>3017</sup> WO ’118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective component”).

1 DHA-E) are not particularly limited as long as intended effects of the present invention are  
2 attained.”<sup>3018</sup> It further states that “the composition is preferably the one having a high purity of  
3 EPA-E and DHA-E.”<sup>3019</sup> Further, WO ’118 does not disclose EPA’s effect on LDL-C, VLDL-C,  
4 Apo-B, or Lp-PLA2.

5 WO ’900 is directed to a process for producing purified EPA from a culture of micro-  
6 organisms. WO ’900 fails to disclose the claimed subject with the specified very high TG levels  
7 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed  
8 pharmaceutical composition with the specified dosage or administration period, or the claimed  
9 method to effect the specified TG reduction without substantially increasing LDL-C. WO ’900  
10 only discloses the method of producing purified EPA for therapeutic use, it does not teach  
11 *administration* of pure EPA. WO ’900 has no discussion, for example, regarding claimed patient  
12 population or method of treatment.

13 WO ’900 does not teach administration of pure EPA to treat hypertriglyceridemia. It  
14 lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one  
15 of them.<sup>3020</sup> Moreover, WO ’900 does not teach the desired effect of EPA other than  
16 commenting generally that it “may promote health and ameliorate or even reverse the effects of a  
17 range of common diseases.”<sup>3021</sup> It has no discussion, for example, on any TG-lowering effect of  
18 EPA. Although WO ’900 identifies DHA as an “undesired molecule”, it does not identify the  
19 *specific* undesired effect of DHA or other impurities it is trying to prevent other than  
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21 <sup>3018</sup> WO ’118 at 22-23.

22 <sup>3019</sup> WO ’118 at 23.

23 <sup>3020</sup> *See, e.g.*, ’900 Pub. at 16-17.

24 <sup>3021</sup> ’900 Pub. at 5.



1 any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>3025</sup>  
2 Defendants’ unsupported cobbling of selective disclosures represents hindsight  
3 reconstruction.<sup>3026</sup> Defendants’ contentions are no more than an assertion that certain claim  
4 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to  
5 establish *prima facie* obviousness.

6 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that  
7 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank  
8 and Mori 2000 in Section V.F.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank  
9 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and  
10 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does  
11 not offer any disclosure regarding the effect of EPA and DHA separately or gain any  
12 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000  
13 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is  
14 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation  
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17 <sup>3025</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
21 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
22 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
23 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
24 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3026</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 to combine with WO '118 or WO '900. Engaging in hindsight bias, Defendants ignore, without  
2 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants  
3 fail to identify any other basis upon which a person of ordinary skill would have sought to  
4 combine Mori 2000 with the Lovaza PDR.

5 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it  
6 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants  
7 ignore, without explanation, other studies that demonstrate that DHA decreases or has little  
8 effect on LDL-C levels.<sup>3027</sup> Defendants identify no other basis upon which a person of ordinary  
9 skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or  
10 Mori.

11 (ii) The '446 Patent is not Obvious Over WO  
12 '118, WO '900, Grimsgaard, Mori 2000  
13 and/or Maki in Combination with the  
14 Omacor PDR/Lovaza PDR, and Further in  
View of Katayama, Matsuzawa and/or  
Takaku.

15 With respect to the '446 Patent, Defendants present a combination of nine references:  
16 "WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment  
17 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view  
18 of Katayama, Matsuzawa and/or Takaku."<sup>3028</sup> Defendants also present charts arguing that an  
19 additional 56 references may be combined in order to render the Claims obvious. Not only do  
20 Defendants ignore the improbability that a person of ordinary skill would combine 56 separate  
21 references, they additionally do not identify any motivation for combining these references.

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23 <sup>3027</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>3028</sup> Defendants' Joint Invalidity Contentions at 443.



1 Although Defendants need not point to an explicit statement in the prior art motivating the  
2 combination of these references, any assertion of an “apparent reason” to combine must find a  
3 basis in the factual record.<sup>3029</sup> Defendants’ unsupported cobbling of selective disclosures  
4 represents hindsight reconstruction.<sup>3030</sup> Defendants’ contentions are no more than an assertion  
5 that certain claim elements were known in the prior art. Throughout their contentions,  
6 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
7 even the reference as a whole. Each reference, however, must be evaluated for all that it  
8 teaches.<sup>3031</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
9 obviousness.

10 The discussion related to WO ‘118 and WO ‘900 in Section V.F.3.c.1.b.i is incorporated  
11 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section  
12 V.F.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and  
13 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”  
14 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the  
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16 <sup>3029</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3030</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>3031</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 very high TG patient population. Neither Grimsgaard nor Mori 2000 provides motivation to  
2 administer 4g/day EPA to the very high TG patient population. Defendants identify no other  
3 basis upon which a person of ordinary skill would have sought to combine the composition  
4 disclosed in Grimsgaard or Mori 2000.

5 Defendants argue that it “would have been obvious to a person of ordinary skill in the art  
6 to use EPA as described in WO ’118, WO ’900, Grimsgaard or Mori 2000 in the treatment  
7 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their  
8 assertions fail to provide a motivation for combining the references.<sup>3032</sup> Although Defendants  
9 need not point to an explicit statement in the prior art motivating the combination of these  
10 references, any assertion of an “apparent reason” to combine must find a basis in the factual  
11 record.<sup>3033</sup> Defendants’ assertions related to motivation are insufficient,<sup>3034</sup> and accordingly  
12 Defendants fail to meet their burden to establish *prima facie* obviousness.

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15 <sup>3032</sup> Defendants’ Joint Invalidation Contentions at 443.

16 <sup>3033</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3034</sup> For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating  
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any  
basis for that statement. While the paragraph associated with that statement makes assertions regarding the  
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO  
’118. See Defendants’ Joint Invalidation Contentions at 444.

1 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or  
2 Takaku. However, they've failed to provide any factual or legal basis as to why each reference  
3 discloses a claim element, an "apparent reason" or motivation to combine the elements in the  
4 manner claimed,<sup>3035</sup> or "a reasonable expectation of success"<sup>3036</sup> of achieving the claimed  
5 invention. Therefore, Defendants should be precluded from relying on these references.

6 As discussed above in Section V.F.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only  
7 designed to confirm the safety of long term treatment of Epadel and its ability to lower both  
8 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer  
9 purified EPA to the very high TG patient population and do not provide any reasonable  
10 expectation of success in lowering TG levels in the very high TG patient population without  
11 increasing LDL-C. As discussed above in Section V.F.3.c.1.a.ii.a.i, Takaku candidly  
12 acknowledges that "only a few subjects were examined" and cautions against drawing a  
13 conclusion "only from the results of the present study."<sup>3037</sup> Further, the study did not include any  
14 placebo control, therefore, a person of ordinary skill in the art would understand these reports do  
15 not provide the ability to conclude that the observed lipid effects would have occurred  
16 independent of the drug that is administered. In addition, the study was conducted exclusively in  
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19 <sup>3035</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 <sup>3036</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, "P&G");  
22 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
23 combination of elements "must do more than yield a predictable result;" combining elements that work together "in  
an unexpected and fruitful manner" would not have been obvious).

24 <sup>3037</sup> Takaku at ICOSAPENT\_DFNDT00006897.

1 Japanese patients, and a person of ordinary skill would not have expected the results to be  
2 applicable to the general population.<sup>3038</sup>

3 The proposed combination does not render the independent claim of the '446 Patent  
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
5 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and  
6 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.<sup>3039</sup>

7 The analysis of the independent claim of the '446 patent is incorporated into all asserted  
8 claims that depend from this Claim.

9 (a) Grimsgaard, Mori 2000 and/or Maki  
10 Do Not Disclose Purported  
11 Knowledge that DHA was  
12 Responsible for the Increase in LDL-  
13 C

12 Defendants contend that a "person of ordinary skill in the art would have been motivated  
13 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known  
14 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is  
15 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or  
16 Maki."<sup>3040</sup>

17 Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose  
18 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,  
19 Mori 2000 and/or Maki in Section V.F.3.c.1.a.ii.a.iii is incorporated herein by reference. A

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21 <sup>3038</sup> Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.")

22 <sup>3039</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that "the  
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").

24 <sup>3040</sup> Defendants' Joint Invalidity Contentions at 443.

1 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA  
2 and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is,  
3 there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although  
4 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not  
5 disclose administration of DHA to the requisite patient population and teaches that DHA is  
6 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,  
7 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
8 would consider. Most controlled studies in patients with normal to high baseline TG levels  
9 indicated that DHA had little or no effect on LDL-C.<sup>3041</sup> Therefore, a person of ordinary skill  
10 would not have concluded that DHA increases LDL-C in patients with normal to high baseline  
11 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is  
12 administered to patients with below-average levels of HDL-C levels and borderline-high TG  
13 levels, a significant increase in LDL-C is observed.<sup>3042</sup> However, one of ordinary skill in the art  
14 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.<sup>3043</sup>  
15 Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

16 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion  
17 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
18 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
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20 <sup>3041</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
21 controlled, found an increase in LDL-C after DHA administration.

22 <sup>3042</sup> Maki at 195.

23 <sup>3043</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*  
*Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A  
24 number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated  
fat and cholesterol, both of which are known to elevate LDL-C.”).

1 has little effect on LDL-C levels.<sup>3044</sup> Defendants identify no other basis upon which a person of  
2 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,  
3 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

4 (iii) A Person of Ordinary Skill Would Not Have  
5 Been Motivated to Administer Purified EPA  
6 in the Treatment Regimen Recited in the  
7 Claims

8 For an invention to be obvious, there must have been an “apparent reason” to make it.  
9 Defendants assert that a “person of ordinary skill in the art would have been motivated to  
10 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to  
11 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>3045</sup> However, as  
12 set forth below, Defendants fail to address why a person of ordinary skill in the art would have  
13 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides  
14 greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering  
15 triglycerides *without increasing LDL-C levels*.

16 Indeed, a person of ordinary skill in the art would have understood that omega 3-fatty  
17 acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG  
18 patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not  
19 have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without  
20 increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients

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23 <sup>3044</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>3045</sup> Defendants’ Joint Invalidity Contentions at 444.

Fibrate <sup>3046</sup>	-20%	+45%
Lovaza/Omacor <sup>3047</sup>	-6%	+45%

That Epadel has been approved for decades but not approved for use in the very high TG patient population prior to the invention of the asserted patents is a real-world reflection of the lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been countless studies conducted which administer Epadel and report the effects observed. Although a few studies administer Epadel to a patient population which included a few patients with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

Defendants further argue that the disclosure in WO '118 would combine with the prior art concerning Lovaza for at least two reasons; first, "products containing DHA were reported to increase LDL-C levels while products containing only EPA did not," and second, "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA."<sup>3048</sup> Both of the "reasons" identified by Defendants are false.

Regarding Defendants' first reason, that "products containing DHA were reported to increase LDL-C levels while products containing only EPA did not," most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.<sup>3049</sup> Therefore, a person of ordinary skill would not have concluded that DHA increases

<sup>3046</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

<sup>3047</sup> Chan 2002 I at 2381 (Table 3).

<sup>3048</sup> Defendants' Joint Invalidity Contentions at 444.

<sup>3049</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

1 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,  
2 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,  
3 while EPA does not.”<sup>3050</sup> First, Leigh-Firbank cannot comment on the effect of EPA and DHA  
4 alone because it did not administer EPA and DHA separately.<sup>3051</sup> A person of ordinary skill  
5 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect  
6 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA  
7 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with  
8 other saturated and polyunsaturated fatty acids.<sup>3052</sup> Therefore, a person of ordinary skill would  
9 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear  
10 how much of the supplement’s effects can be attributed to DHA.<sup>3053</sup> Kelley does not show that  
11 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a  
12 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase  
13 was induced by fibrate therapy.<sup>3054</sup> Kelley specifically teaches that the increase in LDL-C  
14 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel  
15 increase in overall LDL particle number. Rather than concluding that DHA was uniquely  
16 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to  
17 disclose that DHA had uniquely beneficial cardioprotective effects.<sup>3055</sup> Finally, Theobald also

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19 \_\_\_\_\_  
<sup>3050</sup> Defendants’ Joint Invalidation Contentions at 449.

20 <sup>3051</sup> The discussion related to Leigh-Firbank in Section V.F.3.c.1.a.i.a.iii is incorporated herein by reference.

21 <sup>3052</sup> The discussion related to Kelley in Section V.F.3.c.1.a.iii.a.ii is incorporated herein by reference.

22 <sup>3053</sup> *See Mori* 2006 at 96.

23 <sup>3054</sup> Kelley at 329.

24 <sup>3055</sup> Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular health.”)



1 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for  
2 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by  
3 7% when compared to placebo. However, the DHA composition that was administered in  
4 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,  
5 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA  
6 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it  
7 impossible to determine whether or how much of the supplement's effects can be attributed to  
8 DHA.<sup>3056</sup> Contrary to Defendants' assertion that there was "a reported advantage to using EPA  
9 vs. DHA in hypertriglyceridemic subjects,"<sup>3057</sup> there was no known advantage to using EPA vs.  
10 DHA. In fact, a number of the references Defendants cite in their contentions ultimately  
11 conclude that DHA supplementation "may represent a more favorable lipid profile than after  
12 EPA supplementation."<sup>3058</sup> In addition, a person of ordinary skill would have recognized any  
13 impact of DHA reported by the study to be applicable to EPA because they would have  
14 understood these substances to function by the same mechanism. Furthermore, as discussed  
15 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in  
16 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients  
17 because patients with higher TG levels had different lipid responses compared to patients with  
18 lower TG levels.

19           Regarding Defendants' second reason, that "WO '118 reports a reduction in  
20 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,"

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22 <sup>3056</sup> See Mori 2006 at 96.

23 <sup>3057</sup> Defendants' Joint Invalidation Contentions at 444.

24 <sup>3058</sup> Mori 2000 at 1092.

1 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been  
2 well documented.<sup>3059</sup> Lovaza/Omacor has been shown to reduce the risk for cardiovascular  
3 death plus nonfatal myocardial infarction and nonfatal stroke.<sup>3060</sup> Omega-3 fatty acids have been  
4 shown to exert cardioprotective effects in both primary and secondary coronary heart disease  
5 prevention trials.<sup>3061</sup> Omega-3 fatty acids were known to reduce TG concentration, have  
6 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure  
7 and/or reduce heart rate.<sup>3062</sup>

8 Defendants argue that a “person of ordinary skill in the art would have appreciated the  
9 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce  
10 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of  
11 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”<sup>3063</sup> As  
12 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA  
13 and Lovaza/Omacor have been well documented.<sup>3064</sup>

14 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart  
15 disease endpoints as a function of tissue FA composition found that the evidence suggested that  
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17 <sup>3059</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
18 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA  
19 and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

20 <sup>3060</sup> See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,  
21 98 *AM. J. CARDIOL* 71i (2006) (“Bays 2006”).

22 <sup>3061</sup> Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,  
23 197 *ATHEROSCLEROSIS* 12, 13 (2008) (“Harris 2008”).

24 <sup>3062</sup> Harris 2008 at 13.

<sup>3063</sup> Defendants’ Joint Invalidity Contentions at 445.

<sup>3064</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
*ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA  
and CHD risk.”) (“Harris 2007”).

1 DHA is *more* cardioprotective than EPA.<sup>3065</sup> This study found that “depressed levels of long-  
2 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary  
3 heart disease events.”<sup>3066</sup> Further, the study found that DHA levels, with or without EPA, were  
4 significantly lower in fatal endpoints.<sup>3067</sup> This study suggests that DHA is preferable to EPA—  
5 thus teaching away from the claimed invention.<sup>3068</sup> Defendants rely on hindsight bias to argue  
6 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA  
7 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA  
8 was *more* cardioprotective than EPA.

9 Defendants argue that the following claim elements were known: the administration of  
10 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the  
11 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to  
12 patients with high and very high TG levels who were not receiving concurrent lipid altering  
13 therapy, and the dose of 4g/day and 12-week regimen.<sup>3069</sup> Defendants then argue that the “only  
14 question is whether one skilled in the art would have been motivated to use the DHA-free,  
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18 <sup>3065</sup> Harris 2007 at 8.

19 <sup>3066</sup> *Id.*

20 <sup>3067</sup> Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all  
studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

21 <sup>3068</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of  
ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the  
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*  
22 *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs.,*  
*Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the  
23 prior art ... is strong evidence of nonobviousness.”).

24 <sup>3069</sup> Defendants’ Joint Invalidity Contentions at 446.

1 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at  
2 least 500 mg/dL as part of the claimed dosage regimen.”<sup>3070</sup>

3 Defendants’ contentions are no more than a recitation that certain claim elements were  
4 known in the prior art. Defendants’ assertions to the contrary represent hindsight  
5 reconstruction.<sup>3071</sup> Notably, Defendants *do not* assert that a person of ordinary skill would have  
6 known that purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL),  
7 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,<sup>3072</sup>  
8 which included a small minority of patients with baseline TG levels  $> 500$  mg/dL to argue that “a  
9 number of prior art references disclosed the administration of purified EPA to patients with TG  
10 levels  $> 500$  mg/dL.”<sup>3073, 3074</sup> The disclosures of Nakamura (one patient), Matsuzawa (disclosure  
11 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the  
12 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of  
13 ordinary skill in the art would *not* understand these references to relate to the use of EPA in  
14 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions  
15 regarding these references in terms of the very high TG patient population. In Nakamura, one  
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18 <sup>3070</sup> Defendants’ Joint Invalidity Contentions at 446.

19 <sup>3071</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
20 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

21 <sup>3072</sup> Nakamura, Matsuzawa, and Takaku.

22 <sup>3073</sup> Defendants’ Joint Invalidity Contentions at 446.

23 <sup>3074</sup> Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels  $> 500$   
24 mg/dL. Hayashi states that the baseline TG level was  $300 \pm 233$  mg/dL. However, the standard error is unusually  
high and there is no specific disclosure of a single subject with TG levels  $> 500$  mg/dL. Okumuara specifically  
states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

1 patient had a baseline TG level > 500 mg/dL.<sup>3075</sup> However, the mean baseline TG for all patients  
2 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was  
3 well below 500 mg/dL.<sup>3076</sup> In Matsuzawa, three patients had TG levels between 400 and 1000  
4 mg/dL and one patient had TG levels > 1,000 mg/dL.<sup>3077</sup> Based on this disclosure, only one  
5 patient definitively had a baseline TG level  $\geq$  500 mg/dL. Further, this one patient was excluded  
6 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol  
7 made it impossible to assess triglyceride levels.”<sup>3078</sup> In Takaku, three patients had baseline TG  
8 levels above 500 mg/dL.<sup>3079</sup> However, the mean baseline TG level for all patients was 245  
9 mg/dL.<sup>3080</sup> Indeed, the mean baseline TG level of the patients in all three studies was well below  
10 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be  
11 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,  
12 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the  
13 Friedewald’s Equation cannot be used for patients with triglyceride levels  $\geq$  400 mg/dL.<sup>3081</sup>  
14 Defendants have failed to identify all of the claimed elements and fail to provide motivation to  
15 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with  
16 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

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19 <sup>3075</sup> Nakamura at 23, Table 1.

20 <sup>3076</sup> Nakamura at 23, Tables 1 and 2.

21 <sup>3077</sup> *Id.* at 23.

22 <sup>3078</sup> *Id.* at 10.

23 <sup>3079</sup> Takaku at ICOSAPENT\_DFNDTS00006895.

24 <sup>3080</sup> Takaku at ICOSAPENT\_DFNDTS00006875.

<sup>3081</sup> *See* Matsuzawa at ICOSAPENT\_DFNDTS00006450.

1 Defendants contend that a “person of ordinary skill in the art would have been motivated  
2 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the  
3 known TG-lowering effects of highly-purified EPA-E.”<sup>3082</sup> This argument is flawed. The prior  
4 art demonstrates a wide range of administration periods utilized in different clinical studies. For  
5 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in  
6 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.  
7 Given the large number of choices of administration periods disclosed in prior art, Defendants  
8 have not shown that a person of ordinary skill would not have been motivated to administer  
9 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

10 Moreover, a person of ordinary skill would not have been motivated to administer highly-  
11 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as  
12 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood  
13 triglycerides.<sup>3083</sup> In fact, Defendants acknowledge in their Joint Invalidity Contentions that  
14 “DHA and EPA were both known to comparably reduce triglycerides, independently of one  
15 another.”<sup>3084</sup> Data from some studies even suggested that DHA or fish oil may reduce  
16 triglyceride more effectively than EPA.<sup>3085</sup> Therefore, a person of ordinary skill would not have  
17 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination  
18 of EPA and DHA (such as Lovaza) for 12 weeks.

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<sup>3082</sup> Defendants’ Joint Invalidity Contentions at 447.

21 <sup>3083</sup> Mori 2006 at 98.

22 <sup>3084</sup> Defendants’ Joint Invalidity Contentions at 451.

23 <sup>3085</sup> Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor  
24 (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was  
grater with DHA supplementation than EPA supplementation).

1 Defendants argue that a “person of ordinary skill in the art also would have been  
2 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant  
3 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.<sup>3086</sup> This  
4 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with  
5 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to  
6 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

7 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have  
8 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such  
9 as Lovaza).

10 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses  
11 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of  
12 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a  
13 dose of 4 g/day rather than a lower dose.”<sup>3087</sup> A person of ordinary skill would not have relied  
14 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,  
15 because these studies were not designed to determine the effect of dose on the degree of TG  
16 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower  
17 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

18 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood  
19 triglycerides.<sup>3088</sup> Therefore, a person of ordinary skill would not have been motivated to  
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<sup>3086</sup> Defendants’ Joint Invalidation Contentions at 447.

23 <sup>3087</sup> Defendants’ Joint Invalidation Contentions at 447.

24 <sup>3088</sup> See Section III.

1 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of  
2 EPA and DHA (such as Lovaza).

3 Defendants further argue that a “person of ordinary skill in the art would have also been  
4 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with  
5 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much  
6 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito  
7 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”<sup>3089</sup> This  
8 argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a  
9 greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill  
10 would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any  
11 other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects  
12 having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have  
13 expected that a greater decrease in TG levels, in the very high TG patient population, would lead  
14 to a greater increase in LDL-C levels.

15 Defendants contend that a “person of ordinary skill in the art would have been motivated  
16 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a  
17 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to  
18 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”<sup>3090</sup> Defendants first  
19 support this argument by asserting that a person of ordinary skill in the art would have known  
20 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is  
21 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA  
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23 <sup>3089</sup> Defendants’ Joint Invalidity Contentions at 447.

24 <sup>3090</sup> Defendants’ Joint Invalidity Contentions at 438.



1 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,  
2 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in  
3 V.B.4. and 5” to support this proposition,<sup>3091</sup> however these references do not disclose or suggest  
4 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very  
5 high TG patients.<sup>3092</sup>

6 Defendants next argue again that DHA was known to be responsible for the increase in  
7 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of  
8 ordinary skill would understand that both EPA and DHA function similarly, and that both would  
9 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would  
10 increase LDL-C levels in patients with very high TGs.

11 Defendants argue that a person of ordinary skill in the art “would have known that an  
12 increase in LDL-C was an adverse health effect to be avoided.”<sup>3093</sup> While an increase in LDL-C  
13 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that  
14 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3  
15 fatty acids generally, was related to increased conversion of VLDL to LDL particles.<sup>3094</sup>

16 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the  
17 art would have been motivated, with a reasonable expectation of success, to administer a highly-  
18 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in  
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20 <sup>3091</sup> Defendants’ Joint Invalidation Contentions at 448-49.

21 <sup>3092</sup> *See* Section IV.

22 <sup>3093</sup> Defendants’ Joint Invalidation Contentions at 450.

23 <sup>3094</sup> *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription  
24 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly  
converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride  
levels when given prescription omega-3 therapy”); Chan 2003.

1 LDL-C with DHA.”<sup>3095</sup> However, a person of ordinary skill in the art expected an increase in  
2 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time  
3 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant  
4 decrease in the production of VLDL particles and a significant increase in the conversion of  
5 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by  
6 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.<sup>3096</sup> A  
7 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering  
8 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering  
9 mechanism of omega-3 fatty acids.<sup>3097</sup> The discussion related to the TG-lowering mechanism of  
10 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

11 Further, a person of ordinary skill in the art would have understood that EPA therapy  
12 would *not* reduce Apo-B<sup>3098</sup> (which is a reflection of total atherogenic lipoproteins)<sup>3099</sup> in very  
13 high TG patients, and accordingly would not have been motivated to administer the claimed EPA  
14 composition to the very high TG patient population.

15 Accordingly, a person of ordinary skill would not have been motivated to combine WO  
16 ‘118, WO ‘900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and  
17 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not  
18 have been motivated to combine WO ‘118 or WO ‘900, with the Lovaza PDR, or with Leigh-  
19 Firbank and/or Mori 2000.

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21 <sup>3095</sup> Defendants’ Joint Invalidity Contentions at 451.

22 <sup>3096</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”).

23 <sup>3097</sup> Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

24 <sup>3098</sup> *see* Section V.O.

<sup>3099</sup> *see* Section III.

1 (iv) A Person of Ordinary Skill Would Not Have  
2 Had a Reasonable Expectation of Success  
3 with the Combinations Defendants  
4 Hypothesize

5 Defendants contend that a “person of ordinary skill in the art would have been motivated  
6 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal  
7 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>3100</sup>

8 Defendants also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . .  
9 would have given a person of ordinary skill in the art a reasonable expectation of successfully  
10 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in  
11 these subjects relative to baseline or placebo.”<sup>3101</sup> However, Defendants provide no evidence  
12 that a person of ordinary skill would have had a reasonable expectation of success in a method of  
13 reducing triglycerides in a subject having very-high triglyceride levels by administering purified  
14 EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore,  
15 Defendants fail to provide a reasonable expectation of success for the claimed invention.

16 Defendants further argue, that “because it was known that DHA and EPA were  
17 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have  
18 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified  
19 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been  
20 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition  
21 with a reasonable expectation of success that such administration would result in reducing  
22 triglycerides while avoiding an increase in LDL.”<sup>3102</sup> Defendants argument is without any basis.

23 <sup>3100</sup> Defendants’ Joint Invalidity Contentions at 444.

24 <sup>3101</sup> Defendants’ Joint Invalidity Contentions at 448.

<sup>3102</sup> Defendants’ Joint Invalidity Contentions at 452.

1 To the contrary, because a person of ordinary skill in the art would have understood DHA and  
2 EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have  
3 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no  
4 explanation and cite to no article to support their argument that the similar effects on TG levels is  
5 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on  
6 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected  
7 both EPA and DHA, whether administered alone or in combination, would cause an increase in  
8 LDL-C when administered to the very high TG patient population.

9 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients  
10 with very-high TG. A person of ordinary skill would have thus expected EPA, like  
11 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient  
12 population. It was well known that TG-lowering agents, specifically fibrates and  
13 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but  
14 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art  
15 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the  
16 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including  
17 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as  
18 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3103</sup>	-20%	+45%
Lovaza/Omacor <sup>3104</sup>	-6%	+45%

23 <sup>3103</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>3104</sup> Chan 2002 I at 2381 (Table 3).

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Accordingly, a person of ordinary skill would not have a reasonable expectation of success in achieving a reduction in TG levels without substantially increasing LDL-C in patients with very-high TG levels using EPA.

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to the requisite patient population to achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel, which was available for many years prior to the invention of the '446 patent, to patients with very-high TGs as a treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified EPA in the very-high TG population.

Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been countless studies conducted which administer Epadel and report the effects observed. Although a few studies administer Epadel to a patient population which included a few patients with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides.

Accordingly, a person of ordinary skill would not have a reasonable expectation of success in achieving the claimed invention.

1 (2) Dependent Claims

2 (a) Defendants Have Not Shown that Claim 2 of the  
3 '446 Patent Would Have Been Obvious

4 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
5 Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim  
6 by clear and convincing evidence, they also have not adequately proven the obviousness of  
7 Claim 2.

8 Defendants contend that it would be obvious that a person receiving the claimed EPA  
9 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50  
10 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean  
11 LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for  
12 the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) fail to  
13 address whether the specific combination of claim elements were all present in the prior art  
14 references that would have been combined by a person of ordinary skill in the art to produce the  
15 claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie*  
16 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
17 point of reading the element out of the claim. Although convenient and expedient, Defendants'  
18 approach does not conform with the Local Patent Rules of this District, the law of claim  
19 construction, or the law of obviousness.

20 Defendants do not identify any combination of references. Because Defendants do not  
21 identify any combination of references, they necessarily fail to offer any evidence that a person  
22 of skill in the art would be motivated to combine those references in order to achieve the  
23 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of  
24 ordinary skill would have been motivated to combine the elements, other than stating that a

1 patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL  
2 would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously  
3 that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300  
4 mg/dL would be considered hypertriglyceridemic. Plaintiffs note that Defendants fail to provide  
5 specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. Defendants  
6 do not establish that a person of ordinary skill would have been motivated to combine the  
7 elements to achieve the claimed invention.<sup>3105</sup>

8 Similarly, without the disclosure of a combination of references and a motivation/reason  
9 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
10 person of ordinary skill in the art would have had a reasonable expectation of success in  
11 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary  
12 skill would have expected that the combination to work for its intended purpose for treating the  
13 recited patient population.<sup>3106</sup> As such, Defendants fail to demonstrate reasonable expectation of  
14 success of the claimed invention.

15 (b) Defendants Have Not Shown that Claim 3 of the  
16 ‘446 Patent Would Have Been Obvious

17 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
18 Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim  
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21 <sup>3105</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3106</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 by clear and convincing evidence, they also have not adequately proven the obviousness of  
2 Claim 3.

3 Defendants do not identify any combination of references and simply provide a laundry  
4 list of references without explaining how each reference relates to the claimed invention.

5 Defendants further contend, without any support, that a person of ordinary skill would have been  
6 able to determine the patient population in need of the claimed methods of treatment, would seek  
7 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat  
8 those patients having very high triglycerides regardless of the baseline values of these lipids.<sup>3107</sup>

9 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
10 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
11 combination of claim elements were all present in the prior art references that would have been  
12 combined by a person of ordinary skill in the art to produce the claimed invention with a  
13 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
14 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
15 element out of the claim. Although convenient and expedient, Defendants' approach does not  
16 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
17 obviousness.

18 Defendants fail to show a specific combination of references that discloses each element  
19 of the claimed invention. Defendants merely list references, without reference to a specific page  
20 or section, that purportedly disclose disparate elements without explaining how they can be  
21

22  
23 \_\_\_\_\_  
<sup>3107</sup> *Id.*

24  
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1 combined.<sup>3108</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
2 the claimed invention as a whole.<sup>3109</sup> Moreover, by simply identifying prior art references  
3 without discussing the specific teachings of each reference, Defendants fail to consider each  
4 prior art reference as a whole.<sup>3110</sup> Each reference must be evaluated for all that it teaches.  
5 Defendants' unsupported cobbling of selective disclosures represents hindsight  
6 reconstruction.<sup>3111</sup>

7 Because Defendants do not identify any combination of references, they necessarily fail  
8 to offer any evidence that a person of skill in the art would be motivated to combine those  
9 references in order to achieve the invention of the claim as a whole. Defendants make a  
10 conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed  
11 methods of treatment, without providing a reason that would have prompted a person of ordinary  
12 skill to combine the elements.<sup>3112</sup> Such a naked assertion does not show why a person of  
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16 <sup>3108</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
17 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art").

18 <sup>3109</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is  
made with respect to the subject matter as a whole, not separate pieces of the claim").

19 <sup>3110</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("A prior  
20 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention  
in suit.") (internal citation and quotation marks omitted).

21 <sup>3111</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention").

22 <sup>3112</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be  
23 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted)  
24

1 ordinary skill would have been motivated to treat the recited patient population using the claimed  
2 methods of treatment.<sup>3113</sup>

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. In fact, other than simply identifying prior art references that  
7 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
8 ordinary skill would have expected that the combination to work for its intended purpose for  
9 treating the recited patient population.<sup>3114</sup> As such, Defendants fail to demonstrate reasonable  
10 expectation of success of the claimed invention.

11 (c) Defendants Have Not Shown that Claims 4 and 5 of  
12 the '446 Patent Would Have Been Obvious

13 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
14 Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim  
15 by clear and convincing evidence, they also have not adequately proven the obviousness of  
16 Claims 4 and 5.

17 Defendants contend, without support, that the recited reduction in TG represents  
18 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to

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20 <sup>3113</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3114</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of  
2 ordinary skill to seek to reduce TG by the recited amount because there is no significance  
3 attached to the amount. Defendants conclude, without support, that there was a reasonable  
4 expectation of success without identifying any combination of references and without explaining  
5 how each reference relates to the claimed invention.<sup>3115</sup> These contentions: 1) do not assert  
6 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious  
7 analysis; 3) fail to address whether the specific combination of claim elements were all present in  
8 the prior art references that would have been combined by a person of ordinary skill in the art to  
9 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish  
10 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim  
11 element to the point of reading the element out of the claim. Although convenient and expedient,  
12 Defendants' approach does not conform with the Local Patent Rules of this District, the law of  
13 claim construction, or the law of obviousness.

14 Defendants do not identify any combination of references and simply provide a laundry  
15 list of references that purportedly disclose disparate elements without explaining how they can  
16 be combined.<sup>3116</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
17 the claimed invention as a whole.<sup>3117</sup> Defendants selectively cite to an unspecified isolated  
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19 <sup>3115</sup> Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris\_Etherton 2002, Kurabayashi, Leigh-  
20 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney  
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,  
21 von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

22 <sup>3116</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

23 <sup>3117</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).  
24

1 disclosure within a reference without considering other disclosures or even the reference as a  
2 whole. Each reference, however, must be evaluated for all that it teaches.<sup>3118</sup> Defendants’  
3 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>3119</sup>

4 Because Defendants do not identify any combination of references, they necessarily fail  
5 to offer any evidence that a person of skill in the art would be motivated to combine those  
6 references in order to achieve the invention of the claim as a whole. Defendants make a  
7 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to  
8 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a  
9 person of ordinary skill to reduce triglycerides by the recited amount.<sup>3120</sup> Defendants’ burden to  
10 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”  
11 attached to the recited TG reduction amount.<sup>3121</sup> Defendants have not met the burden with the  
12 naked assertion that it would have been obvious to seek the claim element.

13 Similarly, without the disclosure of a combination of references and a motivation/reason  
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a

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15 <sup>3118</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

16 <sup>3119</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
17 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

18 <sup>3120</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,  
20 1356-57 (Fed. Cir. 2007) (“While the KSR Court rejected a rigid application of the teaching, suggestion, or  
motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason  
21 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the  
claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.  
22 398, 418 (2007)).

23 <sup>3121</sup> Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been  
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*  
24 case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

1 person of ordinary skill in the art would have had a reasonable expectation of success in  
2 achieving the claimed invention. Defendants make a conclusory statement that there was a  
3 reasonable expectation of success, without providing a support other than merely identifying  
4 prior art references that purportedly disclose disparate elements.<sup>3122</sup> The mere fact that elements  
5 are capable of being physically combined does not establish reasonable expectation of  
6 success.<sup>3123</sup>

7 (d) Defendants Have Not Shown that Claim 6 of the  
8 '446 Patent Would Have Been Obvious

9 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
10 Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim  
11 by clear and convincing evidence, they also have not adequately proven the obviousness of  
12 Claim 6.

13 Defendants offer no reference in support of their contention that this claim is obvious.  
14 Defendants contend, without providing any support, that it would be obvious to one of skill in  
15 the art to administer a composition containing EPA, but containing no DHA, with a reasonable  
16 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These  
17 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;  
18 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of  
19 claim elements were all present in the prior art references that would have been combined by a  
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21 <sup>3122</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
22 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted).

23 <sup>3123</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”).

1 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation  
2 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
3 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
4 Although convenient and expedient, Defendants’ approach does not conform with the Local  
5 Patent Rules of this District, the law of claim construction, or the law of obviousness.

6 Defendants fail to show a specific combination of references that discloses each element  
7 of the claimed invention. None of the cited references discloses administration of the claimed  
8 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
9 combined to teach the administration of the claimed EPA to very high TG patients.<sup>3124</sup>  
10 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
11 considering other disclosures or even the reference as a whole. Each reference, however, must  
12 be evaluated for all that it teaches.<sup>3125</sup> Defendants’ unsupported cobbling of selective disclosures  
13 represents hindsight reconstruction.<sup>3126</sup>

14 Defendants fail to show a motivation or reason to combine or modify the references  
15 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
16 would have been obvious but such a naked assertion does not show why a person of ordinary  
17 skill would have been motivated to combine the references to achieve the claimed invention.<sup>3127</sup>

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19 <sup>3124</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>3125</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>3126</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 <sup>3127</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill

1 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
2 have successfully achieved the claimed invention. In fact, Defendants do not even discuss  
3 whether a person of ordinary skill would have expected that the combination to work for its  
4 intended purpose.<sup>3128</sup> As such, Defendants fail to demonstrate reasonable expectation of success  
5 of the claimed invention.

6 Defendants rely on only one reference in their invalidity contentions with respect to this  
7 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,  
8 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of  
9 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument  
10 and no support for their argument that Theobald makes such a disclosure. Defendants appear to  
11 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all  
12 atherogenic lipoproteins.<sup>3129</sup>

13 Defendants then make the unsupported assertion that “one of ordinary skill in the art  
14 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to  
15 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald  
16 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render  
17 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis  
18 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL  
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21 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
22 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3128</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

<sup>3129</sup> June 26, 2012 Bays Declaration; *see also* Section III.

1 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with  
 2 respect to this claim or Apo-B levels.

3 As discussed above, *see* Section IV, Theobald discloses the administration of a  
 4 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While  
 5 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a  
 6 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of  
 7 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to  
 8 consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following  
 9 administration of the triacylglycerol composition of that reference.<sup>3130</sup>

10 **TABLE 3**  
 Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect <sup>1</sup>
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 <sup>2</sup>	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) <sup>3</sup>
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) <sup>4</sup>
HDL cholesterol (mmol/L) <sup>5</sup>	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) <sup>6</sup>	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
<b>Apolipoprotein B (g/L)</b>	<b>0.84 ± 0.027</b>	<b>0.87 ± 0.026</b>	<b>0.83 ± 0.028</b>	<b>0.84 ± 0.028</b>	<b>0.03 (0.002, 0.055)<sup>7</sup></b>
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) <sup>3</sup>
Weight (kg) <sup>8</sup>	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

15 <sup>1</sup> Mean difference between active treatment and placebo; 95% CI in parentheses.  
 16 <sup>2</sup>  $\bar{x} \pm \text{SEM}$  (all such values);  $n = 38$ .  
 17 <sup>3,4,7</sup> Paired  $t$  test: <sup>3</sup> $P = 0.04$ , <sup>4</sup> $P = 0.004$ , <sup>7</sup> $P = 0.03$ .  
 18 <sup>5</sup> HDL increased in subjects receiving DHA first. Significant treatment × order effect,  $P = 0.005$ .  
 19 <sup>6</sup>  $n = 37$ ; data were log transformed before analysis by paired  $t$  test.  
 20 <sup>8</sup> Weight increased over the entire study period. Significant order × time effect,  $P = 0.001$ .

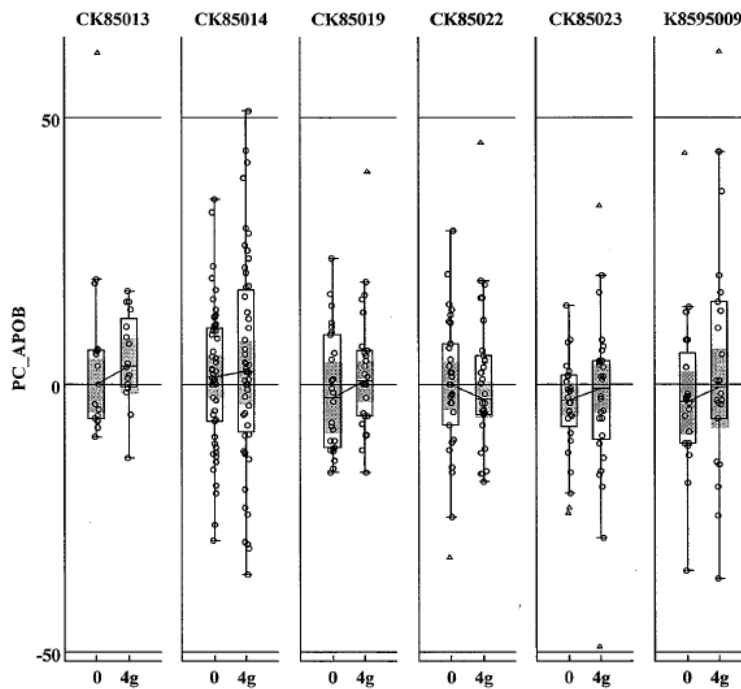
21 As discussed above, *see* Section III, a person of skill in the art would not have  
 22 distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a  
 23 person of ordinary skill would have considered Theobald, they would not conclude from the  
 24 reference that EPA therapy decreases Apo-B levels in very high TG patients.

<sup>3130</sup> Theobald at 561, table 3.



1 A person of skill in the art would *not* have understood that EPA therapy in very high TG  
 2 patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked  
 3 to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on  
 4 Apo-B levels in patients with very high TG levels.<sup>3131</sup> The Lovaza clinical trial, which was a  
 5 large study conducted on patients with very high TG levels, shows no difference between a  
 6 placebo-control group and the treatment group with respect to Apo-B levels.<sup>3132</sup>

14. Box plot of individual Category I studies -% change of APOB



19 In each of these studies, including K8595009, where subjects had a median baseline TG  
 20 level of 818 mg/dL,<sup>3133</sup> there was no change in Apo-B between the control and treatment groups.

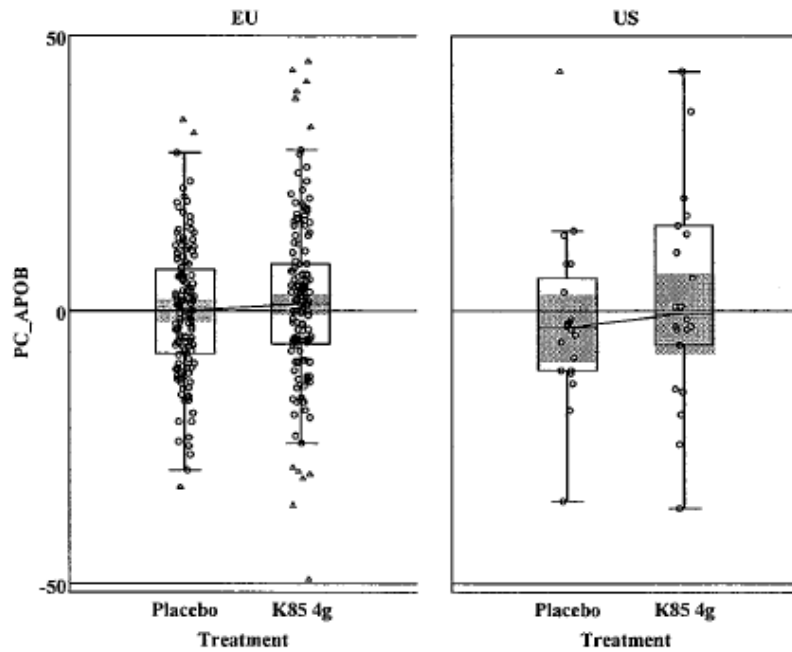
22 <sup>3131</sup> May 8, 2012 Bays Declaration.

23 <sup>3132</sup> Lovaza Approval Package at Table 14.

24 <sup>3133</sup> The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

1 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected  
2 that treatment with Lovaza did not impact Apo-B compared to placebo.<sup>3134</sup>

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4 7. Box plot of pooled Category I studies -% change of APOB



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16 Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-  
17 B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the  
18 literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.<sup>3135</sup>  
19 While Theobald does not even support Defendants' obviousness arguments, their selective  
20 citation of that reference represents impermissible hindsight bias. The examiner had before him  
21 a large number of prior art references reporting Apo-B effects and, even as defendants concede,  
22

23 <sup>3134</sup> Lovaza Approval Package at Table 7.

24 <sup>3135</sup> See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 | agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of  
2 | those references, also reflecting a lack of motivation and no reasonable expectation of  
3 | success.<sup>3136</sup>

4 | Further, a person of skill in the art would have understood Apo-B to be a surrogate for the  
5 | number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.<sup>3137</sup> The person of  
6 | skill in the art would also have recognized that, as TG levels in patients with very high TG levels  
7 | rose, an increasing amount of TGs in those patients were contained within chylomicrons. As  
8 | discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic  
9 | lipoproteins, but instead smaller, denser particles referred to as remnant.<sup>3138</sup> Accordingly,  
10 | because very high TG patients had increasing levels of TGs stored in chylomicrons and because  
11 | chylomicron processing would not have been understood to yield changes in Apo-B, a person of  
12 | skill in the art would have believed that TG-lowering therapies directed to very high TG patients  
13 | would not significantly impact Apo-B.

14 | Accordingly, a person of ordinary skill in the art would not have been motivated to  
15 | replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art  
16 | have been motivated to administer the EPA composition of the claimed invention to very high  
17 | TG patients. For the same reasons, a person of ordinary skill in the art would not have a  
18 | reasonable expectation of success in achieving the claimed invention.

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23 | <sup>3136</sup> Defendants' Contentions at 236.

24 | <sup>3137</sup> ATP-III at 3170; Bays 2008 I at 395.

<sup>3138</sup> Kwiterovich in Kwiterovich at 4.

1 (e) Defendants Have Not Shown that Claim 7 of the  
2 '446 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
4 Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim  
5 by clear and convincing evidence, they also have not adequately proven the obviousness of  
6 Claim 7.

7 Defendants contend that it would have been obvious to use the claimed composition to  
8 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.  
9 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
10 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
11 combination of claim elements were all present in the prior art references that would have been  
12 combined by a person of ordinary skill in the art to produce the claimed invention with a  
13 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
14 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
15 element out of the claim. Although convenient and expedient, Defendants' approach does not  
16 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
17 obviousness.

18 Defendants do not identify any combination of references. Because Defendants do not  
19 identify any combination of references, they necessarily fail to offer any evidence that a person  
20 of skill in the art would be motivated to combine those references in order to achieve the  
21 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of  
22 ordinary skill would have been motivated to combine the elements.<sup>3139</sup> As such, Defendants fail

23 <sup>3139</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR  
24 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,

1 to demonstrate that there was no motivation to combine the references to achieve the claimed  
2 invention.

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. Defendants make conclusory statements without providing any  
7 support. What is more, Defendants do not even discuss the reasonable expectation of reducing  
8 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of  
9 reducing VLDL-C levels using the claimed methods.

10 (f) Defendants Have Not Shown that Claim 8, 9, 10  
11 and 11 of the '446 Patent Would Have Been  
Obvious

12 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
13 Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim  
14 by clear and convincing evidence, they also have not adequately proven the obviousness of  
15 Claims 8, 9, 10 and 11.

16 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach  
17 the additional claim elements of dependent Claims 8-11. Defendants contend, without providing  
18 any support, that the claim elements are the results of simply optimizing the conditions described  
19 in the prior art and within the purview of the skilled physicians. These contentions: 1) do not  
20 assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an  
21 obvious analysis; 3) fail to address whether the specific combination of claim elements were all

22 \_\_\_\_\_  
23 the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill  
24 in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness  
determination.'" (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 present in the prior art references that would have been combined by a person of ordinary skill in  
2 the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to  
3 establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the  
4 claim element to the point of reading the element out of the claim. Although convenient and  
5 expedient, Defendants' approach does not conform with the Local Patent Rules of this District,  
6 the law of claim construction, or the law of obviousness.

7 Defendants fail to show a specific combination of references that discloses each element  
8 of the claimed invention. None of the cited references discloses administration of the claimed  
9 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
10 combined to teach the administration of the claimed EPA to very high TG patients.<sup>3140</sup>

11 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
12 considering other disclosures or even the reference as a whole. Each reference, however, must  
13 be evaluated for all that it teaches.<sup>3141</sup> Defendants' unsupported cobbling of selective disclosures  
14 represents hindsight reconstruction.<sup>3142</sup>

15 Defendants fail to show a motivation or reason to combine or modify the references  
16 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
17 "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not  
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20 <sup>3140</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
21 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art").

22 <sup>3141</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>3142</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention").

1 show why a person of ordinary skill would have been motivated to combine the references to  
2 achieve the claimed invention.<sup>3143</sup>

3 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
4 have successfully achieved the claimed invention. In fact, other than simply identifying prior art  
5 references that purportedly disclose disparate elements, Defendants do not even discuss whether  
6 a person of ordinary skill would have expected that the combination to work for its intended  
7 purpose.<sup>3144</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
8 claimed invention.

9 **4. The '446 Patent is Not Invalid Under § 112**

10 a) Defendants Have Not Demonstrated that the Claims of the '446  
11 Patent Are Invalid for Indefiniteness

12 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]  
13 the subject matter which the applicant regards as his invention.”<sup>3145</sup> Patent claims are valid in  
14 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the  
15 art about the scope of the invention” in light of the specification and the prosecution history.<sup>3146</sup>

16 \_\_\_\_\_  
17 <sup>3143</sup>*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

19 <sup>3144</sup>*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
20 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

21 <sup>3145</sup> Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and  
they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite  
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions  
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from  
23 supplementing their naked assertions with new basis in the course of the litigation.

24 <sup>3146</sup>*Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

1 The Supreme Court has recognized that “absolute precision is unattainable” in claim language  
2 and “the certainty which the law requires in patents is not greater than is reasonable.”<sup>3147</sup>

3 Defendants allege that a number of terms containing the phrases “about” and  
4 “substantially” are indefinite. Defendants do not provide any reason why these terms are  
5 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,  
6 these terms are routinely used in patent claims, and are not *per se* indefinite.<sup>3148</sup> In particular,  
7 courts have held repeatedly that claims that contain the words “about” and “substantially” are not  
8 indefinite.<sup>3149</sup> Here, a person of ordinary skill would understand with reasonable certainty what  
9 is claimed when the claims are read in light of the specification and prosecution history.<sup>3150</sup>  
10 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being  
11 indefinite.

12 Defendants further allege that the term “a capsule . . . not more than about 3%  
13 docosahexaenoic acid or its esters, by weight of all fatty acids present” is indefinite. They

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14  
15 <sup>3147</sup> *Id.* at 2129.

16 <sup>3148</sup> *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms  
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the  
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.  
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the  
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d  
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe  
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish  
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 <sup>3149</sup> *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim  
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.  
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction  
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy  
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration  
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,  
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching . . . at a rate exceeding about 10% per second” is not  
indefinite).

<sup>3150</sup> *See generally* the ’446 patent and its prosecution history.



1 contend that, because there is no indication of how much of the pharmaceutical composition is  
2 composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in  
3 the composition. This is incorrect. A claim can use a ratio to define amounts of components in a  
4 product, using terms such as “percent by weight.”<sup>3151</sup> In light of the specification and  
5 prosecution history, a person of ordinary skill would understand with reasonable certainty the  
6 range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical  
7 composition in relation to all fatty acids present.<sup>3152</sup> Therefore, these terms are not indefinite and  
8 do not render the claims indefinite.

9 Defendants further contend that the metes and bounds of the phrase “without  
10 substantially increasing LDL-C” are unclear. Defendants do not provide the basis for the  
11 assertion other than stating that it is unclear and the specification does not clarify its meaning.  
12 As discussed above, use of the phrase “substantially” does not render a claim *per se* indefinite.  
13 In light of the specification and the prosecution history, a person of ordinary skill in the art  
14 would know with reasonable certainty the scope of the term “without substantially increasing  
15 LDL-C” and therefore does not render the claims indefinite.<sup>3153</sup>

16 Defendants also allege that it is impossible to ascertain the metes and bounds of “a  
17 placebo control.” A person of ordinary skill, however, would understand the metes and bounds  
18 of the term in light of the specification and the prosecution history.<sup>3154</sup> Moreover, the method of  
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20 <sup>3151</sup> *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at \*5–6 (D.N.J.  
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a  
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at \*10 (E.D. Tex. Apr. 27,  
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total  
23 volume of the solution, with this ratio expressed as a percentage”).

24 <sup>3152</sup> See generally the '446 patent and its prosecution history.

<sup>3153</sup> See generally the '446 patent and its prosecution history.

<sup>3154</sup> See generally the '446 patent and its prosecution history.

1 comparing a subject to placebo control, such as a placebo controlled, randomized, double blind  
2 study, would have been known to a person of ordinary skill at the time of the invention.

3 Therefore, the term does not render the claims indefinite.

4 Finally, Defendants contend that the asserted claims improperly mix methods and  
5 formulations because Plaintiffs' assertion of contributory infringement apparently suggests that  
6 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness  
7 analysis is based on what the claim language informs a person of ordinary skill in the art in light  
8 of the specification and the prosecution history. Defendants do not identify any actual claim  
9 language that mixes methods and formulations. Moreover, contributory infringement may be  
10 asserted and proven when a party sells "a material or apparatus for use in *practicing a patented*  
11 *process . . . knowing the same to be especially made or especially adapted for use in an*  
12 *infringement of such patent.*"<sup>3155</sup> Plaintiffs assert that Defendants' ANDA products will be used  
13 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound  
14 itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are  
15 mistaken and the '446 patent claims are not indefinite for improperly mixing methods and  
16 formulations.

17 b) Defendants Have Not Demonstrated that the Claims of the '446  
18 Patent Are Invalid for Insufficient Written Description

19 The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a  
20 written description of the invention." This requires that the specification "reasonably convey" to  
21 a skilled artisan that the applicant "invented" or "had possession" of the claimed subject matter  
22

23 \_\_\_\_\_  
24 <sup>3155</sup> 35 U.S.C. § 271(c) (emphasis added).

1 when the application was filed.<sup>3156</sup> Support need not be literal<sup>3157</sup>—it may be implicit<sup>3158</sup> or  
2 inherent<sup>3159</sup> in the disclosure. In addition, it is unnecessary to include information that is already  
3 known or available to persons of ordinary skill.<sup>3160</sup>

4 Defendants make three arguments regarding the written description requirement. First,  
5 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack  
6 written description. This is incorrect. The specification of asserted patents literally discloses the  
7 claimed invention.<sup>3161</sup> Moreover, the recited baseline TG levels of the claimed invention appear  
8 in the original claims of the application to which the asserted patent claims priority. Thus, there  
9 is a strong presumption that the claimed invention is adequately described.<sup>3162</sup> Defendants do  
10 not and cannot rebut this presumption. Specifically, the patient population is originally claimed  
11 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500  
12 mg/dl.”<sup>3163</sup> The asserted claims recite the same patient population. Defendants do not contend  
13 that the patient population of the asserted claims is not literally described by the specification  
14

15 <sup>3156</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

16 <sup>3157</sup> *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d  
17 422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

18 <sup>3158</sup> *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866  
19 F.2d at 424–25.

20 <sup>3159</sup> *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

21 <sup>3160</sup> *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,  
22 1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

23 <sup>3161</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
24 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
legal foundation for claiming that species.”).

<sup>3162</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

<sup>3163</sup> See U.S. Application No. 12/702,889.

1 and in the original claims of the application to which the asserted patent claims priority. In fact,  
2 the specification and the provisional patent application claims at the time of filing described  
3 these limitations.<sup>3164</sup> Therefore, Defendants have failed to explain whether and how an aspect of  
4 the claimed invention has not been described with sufficient particularity such that one skilled in  
5 the art would recognize that the applicant had possession of the claimed invention.

6 Second, Defendants contend that “a person of skill in the art would not understand that  
7 the inventor was in possession of a method incorporating [] specific dosages and quantities.”  
8 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the  
9 dosages and quantities of the claimed methods.<sup>3165</sup> Moreover, the dosages and quantities of the  
10 method appear in the claims, as originally filed. Thus, there is a strong presumption that the  
11 claimed invention is adequately described.<sup>3166</sup> Defendants do not and cannot rebut this  
12 presumption. For example, the dosage of the composition was originally claimed as “about 1 g  
13 to about 4g.”<sup>3167</sup> Defendants do not contend that dosages and quantities of the asserted claims  
14 are not literally described by the specification and in the original claims. In fact, the  
15 specification and the provisional patent application claims, at the time of filing, described these  
16 limitations. Therefore, Defendants have failed to explain whether and how an aspect of the  
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<sup>3164</sup> ‘446 patent at 13:29-34; 14:49-51; U.S. Application No. 12/702,889

20 <sup>3165</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
22 legal foundation for claiming that species.”).

23 <sup>3166</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

<sup>3167</sup> See U.S. Provisional Application No. 61/151,291.

1 | claimed invention has not been described with sufficient particularity such that one skilled in the  
2 | art would recognize that the applicant had possession of the claimed invention.

3 |         Third, Defendants appear to suggest, although they have not specifically contended, “a  
4 | person of skill in the art would not understand that the inventor was in possession of a method  
5 | comprising a comparison against” placebo control. Although this allegation does not appear to  
6 | implicate written description, the specification describes such a comparison. Therefore, a person  
7 | of ordinary skill would have understood that the inventor was in possession of a method  
8 | comprising administration of a composition with the recited properties, based on a specific  
9 | comparison of a subject or a population against a placebo control.

10 |         In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,<sup>3168</sup> the court  
11 | elaborated that “possession” means possession as evidenced by disclosure. In this case, the  
12 | specification of asserted patents literally disclose the claimed invention in the specification and  
13 | the claims as originally filed. Thus, an examination of the four corners of the specification from  
14 | the perspective of a person of ordinary skill in the art demonstrates that the inventors of the  
15 | asserted patents were in possession of the claimed invention.

16 |         Defendants conclude by alleging that the specification does not describe anything more  
17 | than what is obvious, and thus does not provide adequate support for any nonobvious claim.  
18 | That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the  
19 | specification; nonobviousness can be supported by post-filing date evidence for example.<sup>3169</sup>  
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21 | <sup>3168</sup> *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

22 | <sup>3169</sup> See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)  
23 | (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is  
24 | incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those  
characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,  
1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained

1 Written description requires only that the specification reasonably conveys that the applicant had  
2 possession of the claimed subject matter when the application was filed. Therefore, whether the  
3 claims are obvious has no bearing on the adequacy of written description.

4 c) Defendants Have Not Demonstrated that the Claims of the '446  
5 Patent Are Invalid for Lack of Enablement

6 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person  
7 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would  
8 require undue experimentation for a person of ordinary skill to make or use the invention.

9 Factors that may be considered include the quantity of experimentation necessary, the amount of  
10 direction or guidance presented, the presence or absence of working examples, the nature of the  
11 invention, the state of the prior art, the relative skill of those in the art, the predictability or  
12 unpredictability of the art, and the breadth of the claims.<sup>3170</sup> The enablement requirement is  
13 separate and distinct from the written description requirement,<sup>3171</sup> and as such a claim does not  
14 require descriptive support in the disclosure as originally filed for it to be enabled.<sup>3172</sup>

15 Defendants make two specific arguments regarding the enablement requirement. First,  
16 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of  
17 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the  
18 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary  
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21 after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.  
22 2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full  
range of an invention is not always achieved at the time of filing the patent application.”).

23 <sup>3170</sup> See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

24 <sup>3171</sup> *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

<sup>3172</sup> MPEP § 2164.

1 skill would be able to determine the amounts of the components in the pharmaceutical  
2 composition without any experimentation, much less undue experimentation.

3 Second, Defendants contend that it would take undue experimentation to obtain the  
4 claimed required results listed in the full scope of the patent claims, including the claimed lipid  
5 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed  
6 method and certainly not undue experimentation. Administration of a recited amount of a recited  
7 composition, for a recited duration, to a specific, recited patient population produces the recited  
8 results. No additional experimentation is required, and Defendants do not explain their  
9 allegation that undue experimentation would be required. Defendants also do not contend that  
10 following the claimed method (each recited element) does not produce the recited results. The  
11 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly  
12 demonstrate that administration of EPA of the recited composition, when administered to  
13 patients with very high TG levels for at least 12 weeks, as specified, produces the recited  
14 results.<sup>3173</sup> Therefore, the claims are not invalid for lack of enablement.

15 Defendants conclude by alleging that the specification does not enable anything more  
16 than what is obvious over the prior art or was known to a person of skill in the art. First,  
17 Defendants do not cite any case or present a legal theory to support this assertion. As such, they  
18 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be  
19 precluded in the future from raising any new legal theory to support this assertion. Moreover,  
20 while the '446 patent's specification enables a person of ordinary skill to obtain the claimed  
21 limitations without undue experiment, the claimed limitations would not have been obvious to a  
22 person of ordinary skill, as discussed in Section V.F.3. Furthermore, Plaintiffs have initiated

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<sup>3173</sup> See VASCEPA Prescribing Information at Table 2.

1 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its  
2 claimed methods.<sup>3174, 3175</sup> Therefore, a person of ordinary skill would have concluded that the  
3 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

4 **G. The '652 Patent**

5 **1. The '652 Patent Claims Eligible Subject Matter Under § 101**

6 Defendants' allegation that the asserted claims of the '652 patent relate to ineligible  
7 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*  
8 case under Section 101 or provide a legal or factual basis to support their allegations.

9 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local  
10 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be  
11 provided.<sup>3176</sup> The bare assertion of invalidity under Section 101 without providing the grounds  
12 for such an allegation and examining the elements of the asserted claims of the '652 patent does  
13 not meet this requirement and thwarts the purpose of the Rules.<sup>3177</sup>

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16 <sup>3174</sup> *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any  
17 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical  
18 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that  
19 the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

20 <sup>3175</sup> See May 16, 2011 Bays Declaration at Appendix B.

21 <sup>3176</sup> See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all  
22 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed  
23 statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

24 <sup>3177</sup> Nor does the preceding paragraph, which provides only a purported summary of the claims of the '652 patent, or  
subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the  
grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,  
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent  
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide  
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those  
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).



1 The inquiry under Section 101 involves a two-step test: first, a court must determine  
2 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical  
3 phenomenon, or abstract idea.<sup>3178</sup> Second, even if the claim is directed to one of these concepts,  
4 it still may be patent eligible and the court must determine what else is part of the claim.<sup>3179</sup>

5 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*  
6 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of  
7 the '652 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]  
8 conventional” steps, and the only novel element related to administering the proper dosage based  
9 on a natural law observation.<sup>3180</sup> However, the claims merely recited this natural law without  
10 reciting any novel application of it.<sup>3181</sup> The Court found that providing protection to such  
11 claims would result in pre-empting “a broad range of potential uses” and excluding others from  
12 using “the basic tools of scientific and technical work.”<sup>3182</sup> A method of treatment claim,  
13 specifying the subjects, dosage levels, composition, and time course does not raise the concerns  
14 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent  
15 protection.<sup>3183</sup>

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17 <sup>3178</sup> *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at  
18 issue are directed to one of those patent-ineligible concepts.”).

19 <sup>3179</sup> *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

20 <sup>3180</sup> *Mayo*, 132 S. Ct. at 1294.

21 <sup>3181</sup> *Id.* at 1301.

22 <sup>3182</sup> *Id.*

23 <sup>3183</sup> *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way  
24 of using an existing drug); see also *Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability  
for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula  
and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d  
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent  
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

1 Defendants suggest that the recited EPA composition of each asserted claim is a naturally  
2 occurring substance. It is not. Even references contained within Defendants’ own contentions  
3 make clear that EPA of the requisite purity and characteristics is not found in nature.<sup>3184</sup> As  
4 expressed by the patents cited in Defendants’ contentions and well-established precedent, for  
5 decades it has been accepted that compositions isolated from nature or purified beyond their  
6 natural state are patent-eligible.<sup>3185</sup> Moreover, Defendants’ assertions are immaterial to a Section  
7 101 defense because method of treatment claims like the ones asserted in this case are patent  
8 eligible even if they are directed to administration of a naturally occurring substance.<sup>3186</sup>

9 To the extent Defendants are arguing that a law of nature both underlies the claims and  
10 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the  
11 claimed effects are the natural result of ingesting a naturally-occurring substance.”<sup>3187</sup> Since the  
12 composition that is the subject of the claims is not naturally occurring, Defendants appear to  
13 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states  
14 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad  
15 characterization of laws of nature.<sup>3188</sup> To say that the claims of the ’652 patent claim a law of  
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17 <sup>3184</sup> See, e.g., U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative  
18 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, e.g., at 26–27).

19 <sup>3185</sup> See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394  
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

20 <sup>3186</sup> *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

21 <sup>3187</sup> See Defendants’ Joint Invalidity Contentions at 343.

22 <sup>3188</sup> See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes  
23 to achieve a desired outcome . . . . That one way of describing the process is to describe the natural ability of the  
24 subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we  
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability  
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to  
aspirin).”).

1 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode  
2 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to  
3 underlying principles of nature” that would “make all inventions unpatentable.”<sup>3189</sup> Indeed, even  
4 those concerned about the implications of *Mayo* on future patents were focused on diagnostic  
5 claims not treatment claims of the type that *Mayo* stated were typical and patentable.<sup>3190</sup>

6 Even if there is some underlying law of nature in the asserted claims, the subject matter  
7 of the '652 patent remains eligible for protection under Section 101. As articulated by *Mayo* and  
8 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to  
9 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to  
10 foreclose from others the use of that equation in conjunction with all of the other steps in their  
11 claimed process.’”<sup>3191</sup> As discussed above, the asserted claims of the '652 patent contain a  
12 novel, unconventional, and specific method of treatment comprising a particularized application  
13 of a nonnaturally occurring substance and does not preempt the use of a law of nature.<sup>3192</sup>

14 Defendants also argue that any argument by Amarin in response to Defendants’ § 112  
15 arguments are further evidence of invalidity under § 101. This argument is without merit. The  
16 claims are enabled and written description is satisfied for the reasons discussed below. In  
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<sup>3189</sup> See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

20 <sup>3190</sup> See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying  
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,  
particularly in the area of diagnostic research.”).

22 <sup>3191</sup> See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 <sup>3192</sup> See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at \*4 (C.D. Cal. July 24, 2012)  
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was  
“just one step in the whole process” claimed by the invention).

1 addition, as discussed above, the asserted claims are not merely a naturally-occurring  
2 phenomena, and thus satisfy the requirements of § 101.

3 **2. The Asserted Claims of the ‘652 Patent Are Not Anticipated by WO**  
4 **‘118**

5 To anticipate, a single prior art reference must sufficiently describe a claimed invention  
6 so that the public is in “possession” of that invention.<sup>3193</sup> Therefore, to anticipate, a reference  
7 must set forth every element of the claim, either expressly or inherently, in as complete detail as  
8 is contained in the claim.<sup>3194</sup> The claim elements must also be “arranged” in the prior art  
9 reference, just as they are in the claim,<sup>3195</sup> rather than as “multiple, distinct teachings that the  
10 artisan might somehow combine to achieve the claimed invention.”<sup>3196</sup> In addition, public  
11 “possession” requires that the prior art enable a person of ordinary skill to make and use the  
12 invention without undue experimentation.<sup>3197</sup> Factors that may be included in this analysis  
13 include the quantity of experimentation necessary, the amount of direction or guidance  
14 presented, the presence or absence of working examples, the nature of the invention, the state of  
15 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,

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<sup>3193</sup> *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

20 <sup>3194</sup> *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.  
21 Cir. 1989).

22 <sup>3195</sup> *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

23 <sup>3196</sup> *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587  
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

24 <sup>3197</sup> *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,  
Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

1 and the breadth of the claims.<sup>3198</sup> This inquiry is objective, and thus evidence of undue  
2 experimentation need not be prior art.<sup>3199</sup>

3 Defendants assert that Claims 1-18 of the '652 Patent are anticipated by the WO '118  
4 reference.<sup>3200</sup>

5 A element-by-element analysis, identifying each element of each asserted claim that is  
6 absent from WO '118, is provided below. The contentions below are incorporated by reference  
7 into Exhibit G, and vice-versa. WO '118 does not anticipate the claims of the '652 patent  
8 because it does not describe, properly arrange, or enable the '652 patent claims.

9 a) WO '118 Does Not Teach Every Element of the Claims of the  
10 '652 Patent

11 (1) WO '118 Does Not Describe the Claimed Lipid Effects

12 It is well established that, for a prior art reference to anticipate, “every element of the  
13 claimed invention must be identically shown in a single reference.”<sup>3201</sup> Moreover, the elements  
14 of the claimed invention must have “strict identity” with the elements of the reference; “minimal  
15 and obvious” differences are sufficient to prevent anticipation.<sup>3202</sup> Here, WO '118 entirely fails  
16 to disclose the following elements of Claim 1 of the '652 Patent: *to effect a reduction in*  
17 *triglycerides without substantially increasing LDL-C compared to baseline.* WO '118 further

18 <sup>3198</sup> *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

19 <sup>3199</sup> *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999  
20 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.  
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822  
F.2d 1074, 1078 (Fed. Cir. 1987).

21 <sup>3200</sup> References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs  
reserve their right to obtain a certified translation of WO '118.

22 <sup>3201</sup> *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*  
*Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

23 <sup>3202</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 entirely fails to disclose the following elements of Claim 10 of the '652 Patent: *effective to*  
2 *reduce said baseline triglyceride level without substantially increasing LDL-C compared to a*  
3 *second patient population having said baseline triglyceride level that has not received the*  
4 *pharmaceutical composition*. Defendants appear to concede that WO '118 does not expressly  
5 teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this  
6 element.<sup>3203</sup> Indeed, Defendants could not set forth any basis for concluding that WO '118  
7 teaches this element because WO '118 does not.

8           Instead, Defendants argue that these elements express the intended result of a method that  
9 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth  
10 below, WO '118 fails to disclose each element of the independent claims of the '652 Patent,  
11 either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method.

12 Defendants also argue that these elements represent inherent, natural properties of EPA, and are  
13 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of  
14 anticipation and claim construction. Further, while Defendants argue that the inherent properties  
15 are exemplified in the prior art, they fail to identify even a single prior art reference that makes  
16 such a disclosure. Defendants cannot point to a single, specific prior art reference because the  
17 claimed pharmaceutical composition has never been administered in the manner claimed to the  
18 claimed patient population. Also, these elements are positively recited in the body of the claim  
19 and therefore cannot be construed as a non-limiting preamble and must be given patentable  
20 weight.

21           Further, Defendants entirely fail to prove that inherently discloses the claimed lipid  
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<sup>3203</sup> Defendants' Invalidation Contentions at 202-204.

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1 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
2 inherently anticipate as a matter of law.”<sup>3204</sup> “[A]nticipation by inherent disclosure is appropriate  
3 only when the reference discloses prior art that must *necessarily* include the unstated  
4 limitation.”<sup>3205</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
5 possibly present’ in the prior art.”<sup>3206</sup> WO ‘118 fails to provide any data related to the lipid  
6 effects of the disclosed invention on patients described in the publication. Therefore, Defendants  
7 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets  
8 the elements of the independent claims every time it is administered.

9 Defendants fail to demonstrate that administration of the claimed EPA compositions  
10 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants  
11 suggests that EPA administration may increase LDL-C.<sup>3207</sup> Rambjor is a clinical study which  
12 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA  
13 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a  
14 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*  
15 decrease TG without increasing LDL-C *every time it is administered*.

16 Therefore, WO ‘118 cannot anticipate the independent claims of the ‘652 patent.  
17 Because the dependent claims include all of the claim elements of the independent claims, WO’  
18 118 cannot anticipate any of the dependent claims as well.

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22 <sup>3204</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>3205</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 <sup>3206</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

<sup>3207</sup> *See, e.g., Rambjor*.

1 (2) WO '118 Does Not Disclose Methods of Treating The  
2 Claimed Patient Population

3 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition  
4 be administered in the manner claimed to the claimed patient population. Defendants attempt to  
5 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is  
6 the introductory clause of a patent claim and includes everything from the beginning of the claim  
7 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the  
8 preamble.

9 A claim preamble has patentable weight if, “when read in the context of the entire claim,  
10 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,  
11 and vitality’ to the claim.”<sup>3208</sup> Additionally, the preamble constitutes a claim element when the  
12 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and  
13 claim body to define the claimed limitation.”<sup>3209</sup>

14 The preamble of the asserted claims is limiting for several reasons. The term “subject” in  
15 the preamble of the independent claims defines and provides antecedent basis for the “subject”  
16 recited in the body of the claims. When reading the claim, one must rely on both the preamble  
17 and the claim body to define the claimed invention.

18 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is  
19 properly construed as a limitation of the claim itself.”<sup>3210</sup> The recitation of a “method of

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21 <sup>3208</sup> *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

22 <sup>3209</sup> *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

23 <sup>3210</sup> *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer*  
24 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases  
“portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a  
necessary and defining aspect of the invention, specifically its portability,” and because the specification and  
prosecution history “emphasize this feature of the invention”).



1 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing  
2 triglycerides in the body of the claim and emphasizes the intentional purpose for which the  
3 method must be performed - to reduce triglycerides.

4 It is clear that “the claim drafter chose to use both the preamble and the body of the claim  
5 to define the subject matter of the claimed invention.”<sup>3211</sup> Thus, the entire preamble in the  
6 independent claims of the ‘652 must contain patentable weight.

7 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.  
8 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be  
9 administered in the manner claimed to the claimed patient population.

10 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,  
11 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**  
12 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the  
13 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence  
14 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and  
15 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden  
16 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest  
17 angina and exercise-induced angina, and destabilization of the angina.”<sup>3212</sup> The invention of WO  
18 ‘118 is intended to be administered to any person in need of prevention of the occurrence of  
19 cardiovascular events, who are typically hypercholesterolemia patients.<sup>3213</sup> WO ‘118 does not  
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<sup>3211</sup> *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

23 <sup>3212</sup> WO ‘118 at 12.

24 <sup>3213</sup> *Id.*

1 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot  
2 anticipate the independent claims.

3 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail  
4 to prove that these elements of the claimed invention have “strict identity” with the elements of  
5 the reference.<sup>3214</sup> WO ‘118 fails to anticipate this claim element because the broad disclosure  
6 fails to anticipate the narrow claimed range, and the specific patient population defined in the  
7 claims is an essential part of the claimed invention.

8 There is no evidence in that subject as described in the claims were ever treated. In fact,  
9 WO ‘118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the  
10 definition of “hypertriglyceridemia” in WO ‘118 to argue that WO ‘118 discloses treatment of  
11 the subject as described in the claims. It does not. Defendants’ argument rests on the definition  
12 in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150  
13 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working  
14 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels  
15 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any  
16 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as  
17 evidence that a “person of ordinary skill in the art would have understood that the term  
18 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of  
19 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable  
20 and then merely provides examples of commercially available “soft capsules,” such as Omacor.  
21 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients  
22 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be

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24 <sup>3214</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’  
2 or ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”<sup>3215</sup> Therefore,  
3 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO  
4 ‘118 meets the claim elements of the independent claims every time it is administered.

5 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges  
6 claimed by the ‘652 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500  
7 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between  
8 330 and 450 degrees. The court found that the broader prior art range could not anticipate the  
9 claimed temperature range, “[g]iven the considerable difference between the claimed range and  
10 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the  
11 claimed range with sufficient specificity to anticipate this element of the claim.”<sup>3216</sup> A prior art’s  
12 teaching of a broad genus does not necessarily disclose every species within that genus. The  
13 court explained the slightly overlapping range between the preferred range and claimed range “is  
14 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>3217</sup> and therefore  
15 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of  
16 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not  
17 anticipate the subject as described in the claims because it fails to described the claimed TG  
18 range with sufficient specificity.

19 The court in *Atofina* ruled on an additional question of anticipation that also involved a  
20 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

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22 <sup>3215</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>3216</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

24 <sup>3217</sup> *Atofina*, 441 F.3d at 1000.

1 compared to the patent’s claimed range of 0.1 to 5.0 percent.<sup>3218</sup> The court explained that  
2 “although there is a slight overlap, no reasonable fact finder could determine that this overlap  
3 describes the entire claimed range with sufficient specificity to anticipate this limitation of the  
4 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”<sup>3219</sup> Similarly,  
5 although there may be overlap between the definition of hypertriglyceridemia taught by WO  
6 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not  
7 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500  
8 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of  
9 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels  
10 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic  
11 events as the primary clinical objective),<sup>3220</sup> WO ‘118, therefore, does not expressly disclose the  
12 specific patient population that is an essential element of the claims of the asserted patents.  
13 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

14 The treatment of a patient with elevated TG levels varies depending on their serum  
15 triglyceride levels. Identification of the patient population with very high TG levels (at least 500  
16 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,  
17 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment  
18 of lipid disorders.<sup>3221</sup> The ATP-III divided hypertriglyceridemia patients into three classes based  
19 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),  
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21 <sup>3218</sup> *Id.*

22 <sup>3219</sup> *Id.*

23 <sup>3220</sup> *See* Section III.

24 <sup>3221</sup> *Id.*

1 and very-high TGs ( $\geq 500$  mg/dL)—and recommended substantially different treatment  
2 strategies for patients depending on classification.<sup>3222</sup> For the borderline-high and high TG  
3 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.<sup>3223</sup>  
4 Accordingly, in these populations, physicians focused on lowering LDL-C.<sup>3224</sup> In this patient  
5 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.  
6 In contrast, the primary goal for very-high TG patients ( $\geq 500$  mg/dL) was to reduce the risk of  
7 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated  
8 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary  
9 treatment goal.<sup>3225</sup> Therefore, as evidenced by the ATP-III, patients with very-high TG levels  
10 were considered fundamentally different from patients with borderline-high or high TGs from a  
11 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

12 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride  
13 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In  
14 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at  
15 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular  
16 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).  
17 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels  
18 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by  
19 decreasing triglycerides), as required by the independent claims of the asserted patents, and  
20 therefore cannot anticipate the independent claims of the ‘652 Patent.

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22 <sup>3222</sup> ATP III at 3335; *See also* Section III.

23 <sup>3223</sup> *Id.*

24 <sup>3224</sup> *Id.*

<sup>3225</sup> *Id.*

1 (3) WO '118 Does Not Describe the Claimed Pharmaceutical  
2 Composition or its Specific Administration

3 WO '118 further does not anticipate the claims of the '652 patent because it does not  
4 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as  
5 claimed, it cannot anticipate oral administration to the claimed "subject."

6 WO '118 additionally cannot anticipate the claims of the '652 patent because it does not  
7 disclose administering the pharmaceutical composition at a dose of about 4g per day.  
8 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is  
9 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which  
10 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more  
11 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8  
12 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is  
13 not particularly limited as long as the intended effect, preventing the occurrence of  
14 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose  
15 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be  
16 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no  
17 working examples, data or other reference in WO '118 indicating that any subject (much less  
18 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the  
19 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

20 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of  
21 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The  
22 court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic  
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1 range of 330 to 450 °C,<sup>3226</sup> and therefore failed to anticipate the claimed range. The court in  
2 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate  
3 the patent’s claimed range of 0.1 to 5.0 percent.<sup>3227</sup> The court explained that “although there is a  
4 slight overlap, no reasonable fact finder could determine that this overlap describes the entire  
5 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are  
6 different, not the same. . . . Thus, there is no anticipation.”<sup>3228</sup> Similarly, although there may be  
7 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘652  
8 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range  
9 claimed by the ‘652 patent does not fall within WO ‘118’s preferred range. Defendants  
10 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,  
11 the example indicates that up to 900 mg of the EPA composition could be used three times per  
12 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘652  
13 patent and cannot anticipate the independent claims of the ‘652 Patent.

14 WO ‘118 further does not anticipate the claims of the ‘652 patent because it does not  
15 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a  
16 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.  
17 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high  
18 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and  
19 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or  
20 higher, and still more preferably 96.5% by weight or higher.”<sup>3229</sup> Therefore, WO ‘118 discloses

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22 <sup>3226</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>3227</sup> *Id.*

24 <sup>3228</sup> *Id.*

<sup>3229</sup> WO ‘118 at 22.

1 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total  
2 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed  
3 generic range for the EPA composition in the claimed pharmaceutical composition.

4 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the  
5 . . . range claimed in the” patent is insufficient for anticipation.<sup>3230</sup> In *Atofina*, the prior art  
6 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a  
7 range between 330 and 450 degrees. The court explained that this slight overlap “is not  
8 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>3231</sup> and therefore failed  
9 to anticipate the claimed range.<sup>3232</sup> The court in *Atofina* also found that a prior art disclosure of a  
10 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0  
11 percent.<sup>3233</sup> The court explained that “although there is a slight overlap, no reasonable fact finder  
12 could determine that this overlap describes the entire claimed range with sufficient specificity to  
13 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no  
14 anticipation.”<sup>3234</sup>

15 Similarly, although there may be some overlap between the E-EPA content disclosed by  
16 WO ‘118 and the ranges claimed by the ‘652 patent, WO ‘118 does not specifically highlight the  
17 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a  
18 critical factor of the invention disclosed in the ‘652 patent. Therefore, WO ‘118’s broad  
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21 <sup>3230</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

22 <sup>3231</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>3232</sup> *Atofina*, 441 F.3d at 1000.

24 <sup>3233</sup> *Id.*

<sup>3234</sup> *Id.*



1 disclosure of the E-EPA content in its invention does not describe the claimed range with  
2 sufficient specificity and cannot anticipate the independent claims of the '652 patent.

3 WO '118 is additionally insufficient for anticipation because it does not expressly  
4 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118  
5 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is  
6 DHA-E."<sup>3235</sup> The disclosure goes on to state that the composition of the invention is preferably  
7 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed  
8 pharmaceutical composition is a critical factor of the invention disclosed in the '652 patent.

9 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed  
10 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.  
11 There is no express teaching or guidance directing the person of ordinary skill in the art to the  
12 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no  
13 difference between the use of EPA or DHA in its invention, cannot anticipate the independent  
14 claims of the '652 patent.

15 Defendants contend that Plaintiffs are estopped from arguing there is any material  
16 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants  
17 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing  
18 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is  
19 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and  
20 Defendants have cited no authority to support their position suggesting the contrary. The  
21 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases  
22 and are not co-extensive. Accordingly, plaintiffs are not estopped.

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<sup>3235</sup> WO '118 at 22.

1 In the same paragraph containing their allegation of estoppel, Defendants also quote from  
2 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their  
3 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these  
4 statements form the basis for any theory of estoppel. To the extent that Defendants quote  
5 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The  
6 quoted statements do not identify any recited claim element, including the specific  
7 pharmaceutical composition, the recited patient population, administration in the manner  
8 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from  
9 the quoted statements.

10 (4) WO '118 Does Not Describe the Dependent Claims

11 Defendants fail to address any of the claim elements of the dependent claims.  
12 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail  
13 to set forth any meaningful basis for concluding that WO '118 teaches these elements.  
14 Defendants further argue that "aspects of the claims relating to effects that are to be achieved by  
15 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to  
16 no patentable weight." To the extent the recited claim elements relate to the administration step,  
17 the dosage form or characteristics of the treated subject and the specific effect produced by the  
18 claimed method, Defendants' contentions that the claim limitations are inherent properties of  
19 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO  
20 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.  
21 Defendants have not met the burden to establish anticipation with the naked assertion that the  
22 effects are inherent, natural properties of EPA.

23 Further, Defendants entirely fail to prove that inherently discloses the recited claim  
24 limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot

1 inherently anticipate as a matter of law.”<sup>3236</sup> “[A]nticipation by inherent disclosure is appropriate  
2 only when the reference discloses prior art that must *necessarily* include the unstated  
3 limitation.”<sup>3237</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
4 possibly present’ in the prior art.”<sup>3238</sup> Defendants fail to show that WO ‘118 “*necessarily*” meets  
5 the recited claim elements relating to the administration step, the dosage form or characteristics  
6 of the treated subject and the specific effect produced by the claimed method *every time*. WO  
7 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total  
8 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in  
9 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,  
10 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and  
11 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim  
12 elements.

### 13 3. The Claims of the ‘652 Patent Would Not Have Been Obvious In 14 Light of the Asserted References

15 Defendants identify 77 separate references that it asserts somehow render the claims of  
16 the ‘652 Patent obvious.<sup>3239</sup> Defendants fail to demonstrate by clear and convincing evidence  
17 that any of these references, alone or in combination, would render obvious any claims of the  
18 ‘652 Patent. Defendants’ arguments rely on hindsight by impermissibly using the blueprint of  
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21 <sup>3236</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

22 <sup>3237</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 <sup>3238</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 <sup>3239</sup> Defendants’ Joint Invalidity Contentions at 13-25.

1 the '652 Patent itself to guide its combination of references.<sup>3240</sup> Defendants chart a laundry list  
2 of 77 separate references, without explanation. Defendants' disclosures do not comply with  
3 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly  
4 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs  
5 cannot respond to undisclosed combinations and arguments.<sup>3241</sup>

6 Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions,  
7 Plaintiffs have discerned and will specifically respond to the following alleged prior art  
8 combinations:

- 9 • 1) “. . .the asserted claims of the '652 patent would have been obvious over the  
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
11 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in  
12 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori  
13 2000.”
- 14 • 2) “. . .the asserted claims of the '652 patent would have been obvious over the  
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
16 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,  
17 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori  
18 2000 and/or Maki.”
- 19 • 3) “. . .the asserted claims of the '652 patent would have been obvious over the  
20 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
21 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view  
22 of Satoh or Shinozaki in further view of Contacos.”
- 23 • 4) “. . . the asserted claims of the '652 patent would have been obvious over WO '118  
24 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the  
Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”

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20 <sup>3240</sup> *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention  
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is  
obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 <sup>3241</sup> This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,  
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for  
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the  
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that  
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to  
rely on undisclosed or insufficiently disclosed references or argument.

- 1
- 2 • 5) “. . . the asserted claims of the ’652 patent would have been obvious over WO
  - 3 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
  - 4 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
  - 5 further in view of Katayama, Matsuzawa and/or Takaku.”

6 A patent claim is invalid “if the differences between the subject matter sought to be

7 patented and the prior art are such that the subject matter as a whole would have been obvious at

8 the time the invention was made to a person having ordinary skill in the art.”<sup>3242</sup> Obviousness is

9 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,

10 (2) the scope and content of the prior art, and (3) the differences between the prior art and the

11 claims at issue.<sup>3243</sup>

12 In evaluating obviousness, each prior art reference must be evaluated for all that it

13 teaches, including the portions that would lead away from the claimed invention.<sup>3244</sup> Indeed, any

14 teaching in the art that points away from the claimed invention must be considered.<sup>3245</sup> A

15 reference teaches away if a person of ordinary skill, upon reading the reference, would be

16 discouraged from following the path set out in the reference, or would be led in a direction

17 divergent from the path that was taken by the applicant.<sup>3246</sup> For instance, a reference teaches

18 away if it suggests that the line of development flowing from the reference’s disclosure is

19 unlikely to be productive of the result sought by the applicant.<sup>3247</sup>

20 <sup>3242</sup> 35 U.S.C. § 103(a).

21 <sup>3243</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

22 <sup>3244</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011).

23 <sup>3245</sup> *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999).

24 <sup>3246</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

<sup>3247</sup> *Id.*

1 In order to find obviousness based on a combination of references, there must be some  
2 rationale for combining the references in the way claimed that is separate and apart from the  
3 hindsight provided by the patented invention itself.<sup>3248</sup> The law prohibits an obviousness  
4 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art  
5 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of  
6 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed  
7 invention.”<sup>3249</sup> “The invention must be viewed not after the blueprint has been drawn by the  
8 inventor, but as it would have been perceived in the state of the art that existed at the time the  
9 invention was made.”<sup>3250</sup>

10 “The determination of obviousness is made with respect to the subject matter as a whole,  
11 not separate pieces of the claim.”<sup>3251</sup> “[A] patent composed of several elements is not proved  
12 obvious merely by demonstrating that each of its elements was, independently, known in the  
13 prior art.”<sup>3252</sup> “This is so because inventions in most, if not all, instances rely upon building  
14 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations  
15 of what, in some sense, is already known.”<sup>3253</sup>

16 Accordingly, it is improper to pick and choose isolated elements from the prior art and  
17 combine them so as to yield the invention<sup>3254</sup> or to modify a prior art reference in a way that

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19 <sup>3248</sup> *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

20 <sup>3249</sup> *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

21 <sup>3250</sup> *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

22 <sup>3251</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

23 <sup>3252</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

24 <sup>3253</sup> *KSR*, 550 U.S. at 418-419.

<sup>3254</sup> *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

1 “would destroy the fundamental characteristics of that reference.”<sup>3255</sup> Moreover, a combination  
2 is not obvious where “it would be impossible to apply these teachings [of the secondary  
3 reference] to the [primary reference] without entirely changing the basic mechanism and  
4 procedure thereof,”<sup>3256</sup> or where the proposed combination requires “material and radical  
5 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the  
6 prior art device.<sup>3257</sup> Furthermore, it is improper “to modify the secondary reference before it is  
7 employed to modify the primary reference” in assessing obviousness.<sup>3258</sup>

8 Further, a party asserting obviousness in view of a combination of prior art disclosures  
9 must show that a person of ordinary skill in the relevant field had an “apparent reason” to  
10 combine the elements in the manner claimed<sup>3259</sup> and “a reasonable expectation of success.”<sup>3260</sup>

11 For chemical compounds, there must have been a reason both to select the prior art  
12 compound “most promising to modify” and to make the necessary changes to arrive at the  
13 claimed compound.<sup>3261</sup> This protects against the use of hindsight to pick through the prior art  
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15 <sup>3255</sup> *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

16 <sup>3256</sup> *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

17 <sup>3257</sup> *Id.* at 88.

18 <sup>3258</sup> *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

19 <sup>3259</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 <sup>3260</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

23 <sup>3261</sup> *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–  
24 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*  
*Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

1 based solely on structural similarity to the claimed compound.<sup>3262</sup> Any assertion of an “apparent  
2 reason” must find a basis in the factual record.<sup>3263</sup>

3 The “reasonable expectation of success” for a chemical compound must be of all of a  
4 claimed compound’s relevant properties,<sup>3264</sup> including those discovered after the patent was filed  
5 or even issued.<sup>3265</sup> “The basic principle behind this rule is straight-forward—that which would  
6 have been surprising to a person of ordinary skill in a particular art would not have been  
7 obvious.”<sup>3266</sup> Any assertion of a “reasonable expectation of success” must find a basis in the  
8 factual record.<sup>3267</sup>

9  
10 <sup>3262</sup> *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at \*14. *Accord In re Vaidyanathan*, 381. 985, 994  
11 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.  
12 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.  
13 2002).

14 <sup>3263</sup> *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions  
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to  
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the  
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at  
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*  
19 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed  
20 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438  
21 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in  
22 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that  
23 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
24 motivated to resolve citalopram in June 1988”).

25 <sup>3264</sup> *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success  
26 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .  
27 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of  
28 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d  
29 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the  
30 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of  
31 pharmacological properties that it possesses.”).

32 <sup>3265</sup> *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at  
33 908.

34 <sup>3266</sup> *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,  
such as chemistry, where minor changes in a product or process may yield substantially different results.”).

<sup>3267</sup> *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Aptex argues that the district court applied an incorrect  
inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were



1 In an obviousness determination, any objective indicia of nonobviousness must be taken  
2 into account.<sup>3268</sup> An objective indicium is any “event[] proved to have actually happened in the  
3 real world” that evidences the nonobvious nature of the invention.<sup>3269</sup> The existence of an  
4 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or  
5 surprising results, expressions of skepticism, industry praise, commercial success, and copying  
6 are classical indicia of nonobviousness.<sup>3270</sup> These factual inquiries “guard against slipping into  
7 use of hindsight,”<sup>3271</sup> and “may often be the most probative and cogent evidence of  
8 nonobviousness.”<sup>3272</sup>

9 Also, as with assertions of anticipation, in order for an invention to be obvious, it must  
10 have been fully “in possession” of the public—which requires that the claimed invention have  
11 been enabled.<sup>3273</sup>

12  
13  
14 unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general  
15 knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955  
16 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.  
17 However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly  
18 expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re*  
19 *May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a  
20 substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

3268 *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

3269 *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

3270 *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*  
19 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750  
20 (Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

3271 *Graham*, 383 U.S. at 36.

3272 *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*  
21 *Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

3273 *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for  
22 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,  
23 399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for  
24 making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound  
itself is in the possession of the public.”).

1 A element-by-element analysis, identifying each limitation of each asserted claim that is  
2 absent from the prior art, is provided below, and also provided at Exhibit G. The contentions  
3 below are incorporated by reference into Exhibit G, and vice-versa.

4 a) General Overview

5 Defendants fail to provide a single prior art reference that discloses administration of the  
6 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population  
7 ( $\geq 500$  mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,  
8 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying  
9 degrees of purity, in a wide range of doses and administration periods, to subjects who have  
10 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance  
11 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo  
12 controlled studies are considered the “gold standard” of clinical studies. Studies involving the  
13 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot  
14 distinguish between the effect of the placebo from that of the active agent. Studies which  
15 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the  
16 independent effects of EPA and DHA.<sup>3274</sup> Inconsistency in dosages and administration periods  
17 and variations in the administered fatty acid compositions also complicate the interpretation of  
18 the results and limit the application of these studies.

19 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with  
20 very high TGs together with patients with high and borderline high TGs indicates that there is no  
21 medical difference in responsiveness to treatment among the groups of people.”<sup>3275</sup> Defendants  
22

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23 <sup>3274</sup> Mori 2006 at 96.

24 <sup>3275</sup> Defendants’ Joint Invalidity Contentions at 354 (see FN 56).

1 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-  
2 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in  
3 patients with high triglycerides ( $\geq 200$  mg/dL and  $< 500$  mg/dL) who were also on statin therapy.  
4 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g  
5 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG  
6 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that  
7 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.<sup>3276</sup> In  
8 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were  
9 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use  
10 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a  
11 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the  
12 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to  
13 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.  
14 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical  
15 difference in responsiveness to treatment between the very-high TG patient population and lower  
16 TG patient populations merely because there was possibly one patient with baseline TG levels of  
17 at least 500 mg/dL.

18 As discussed above in Section III, patients with very-high TG levels were considered  
19 fundamentally different from patients with borderline-high or high TGs from a clinical,  
20 regulatory, and therapeutic perspective.<sup>3277</sup> Clinically, the authoritative guidance to physicians

22 <sup>3276</sup> FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6  
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been  
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline  
TG values < 500 mg/dL).

24 <sup>3277</sup> See Bays Jan. 8, 2012 Decl., ¶ 20.

1 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III  
2 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;  
3 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients  
4 was atherosclerosis, while the primary risk faced by very-high TG patients was acute  
5 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for  
6 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for  
7 very-high TG patients was TG reduction. This distinction between patients with borderline-  
8 high/high TG levels and patients with very high TG levels is also observed on the regulatory  
9 level. The FDA recognized the different clinical status of the very-high TG population by  
10 approving some drugs specifically for the very-high TG group without granting treatment  
11 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).<sup>3278</sup>

12 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the  
13 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the  
14 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known  
15 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the  
16 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG  
17 level of the patient receiving treatment.

18 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but  
19 *increase* LDL-C in very-high TG patients.<sup>3279</sup> The fibrate, Tricor (fenofibrate), for example,  
20 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)<sup>3280</sup>

21  
22 <sup>3278</sup> See Bays Jan. 8, 2012 Decl., ¶ 22.

23 <sup>3279</sup> See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain  
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

24 <sup>3280</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).<sup>3281</sup> In  
 2 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-  
 3 significant increase in LDL-C was observed.<sup>3282</sup> In patients with very-high TGs (mean baseline  
 4 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).<sup>3283</sup> Similar  
 5 results were seen with the administration of Lopid (gemfibrozil).<sup>3284</sup> The differing effects of  
 6 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values  
 7 demonstrates how a person of ordinary skill at the time of the invention would have understood  
 8 that one could not simply assume that an observed effect of a TG-lowering agent on lipid  
 9 parameters in patients with normal, borderline-high or high TG levels would be the same in  
 10 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or  
 11 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with  
 12 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-  
 13 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean  
 14 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level  
 15 of 726 mg/dL) experience significantly increased LDL-C levels.

<b>Fibrate</b>	<b>Mean Baseline TG Value</b>	<b>TG</b>	<b>LDL-C</b>	<b>HDL-C</b>	<b>Total-C</b>
Tricor (fenofibrate) <sup>3285</sup>	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*

3281 *Id.*

3282 *Id.* See also, Trilipix Label at 27.

3283 *Id.* See also, Trilipix Label at 27.

3284 See *Otvos* at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); *Manttari* at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

3285 Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

\* = p < 0.05 vs. Placebo

Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing lipid effects depending on the patient’s baseline TG level. When administered to patients with borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-C.<sup>3286</sup> It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.<sup>3287</sup> However, when administered to patients with very-high baseline TG levels, TGs were reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.<sup>3288</sup> Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>3289</sup>

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG

<sup>3286</sup> Chan 2002 I at 2379-81.

<sup>3287</sup> *Id.*; See also, Westphal at 918.

<sup>3288</sup> See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

<sup>3289</sup> See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”)

1 levels ( $\geq 500$  mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They  
2 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when  
3 the normal, borderline-high or high TG patient populations were administered omega-3 fatty  
4 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was  
5 expected as a natural consequence of lowering TGs. A person of ordinary skill would have  
6 considered the rise in LDL-C to be a direct consequence of TG lowering through increased  
7 VLDL particle conversion.<sup>3290</sup> Because normal to high TG patients did not have the large  
8 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not  
9 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree  
10 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,  
11 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the  
12 highest baseline TG levels<sup>3291</sup> and did not increase for patients with lower TG levels. Therefore,  
13 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,  
14 borderline-high or high TG patients was *expected*.

15 Defendants contend that “a composition and its properties are inseparable, and therefore  
16 do not impart any additional patentability,” and that “all of the limitations regarding the  
17 properties of the ethyl EPA compound identified in the claims of the ‘652 patent are inherent to  
18 the compound when administered to a human subject.”<sup>3292</sup> Inherency may not supply a missing

19 \_\_\_\_\_  
20 <sup>3290</sup> Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class  
21 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels  
22 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during  
treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some  
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the  
decrease in VLDL.”).

23 <sup>3291</sup> Bays 2008 I at 400-402.

24 <sup>3292</sup> Defendants’ Joint Invalidity Contentions at 355.

1 claim limitation in an obviousness analysis unless the inherency would have been obvious to one  
2 of ordinary skill in the art.<sup>3293</sup> Obviousness is based on what is *known* in the art at the time of the  
3 invention.<sup>3294</sup> It was not known or reasonably expected at the time of the claimed invention that  
4 purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL), would not  
5 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and  
6 Apo-B necessarily present, or the natural result of the combination of elements explicitly  
7 disclosed by the prior art.<sup>3295</sup> Therefore, inherency does not supply the missing claim elements  
8 in the prior art cited by Defendants.

9 Defendants argue that the claims of the ‘652 patent which contain “a limiting clause, such  
10 as ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step positively  
11 recited and therefore are not elements.<sup>3296</sup> This is incorrect. “There is nothing inherently wrong  
12 with defining some part of an invention in functional terms.”<sup>3297</sup> When a clause “states a  
13 condition that is material to patentability, it cannot be ignored in order to change the substance of  
14 the invention.”<sup>3298</sup> The claim term “to effect” acts as a positive limitation if the term represents

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17 <sup>3293</sup> See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .  
18 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an  
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of  
19 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere  
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

20 <sup>3294</sup> *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.  
Obviousness cannot be predicated on what is unknown.”).

21 <sup>3295</sup> See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 <sup>3296</sup> Defendants’ Joint Invalidity Contentions at 356.

23 <sup>3297</sup> See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 <sup>3298</sup> *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).



1 “unexpected and improved effects of administration of the claimed compound.”<sup>3299</sup> In addition,  
2 the elements represent unexpected and improved effects of administration of purified EPA,  
3 because a person of ordinary skill would not have expected no substantial increase in LDL-C or  
4 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the  
5 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded  
6 patentable weight.

7 b) Identification of Claim Elements Absent from Each Item of Prior  
8 Art

9 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.  
10 Where a limitation is absent from any Independent Claim, that limitation is absent from all  
11 asserted claims, and that analysis is incorporated by reference into each dependent claim. For  
12 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted  
13 claims is not a concession that such limitation is present in the reference. By discussing  
14 Defendants’ analysis of the “limitations” in the claims, Plaintiffs do not concede that Defendants  
15 have appropriately divided the claim language for any purpose.

16 (1) WO ‘118

17 WO ‘118 discloses a composition containing EPA-E for preventing the occurrence of  
18 cardiovascular events in multiple risk patients.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
20 ‘118 disclose or suggest elements of the ‘652 Claims. The cited portions of WO ‘118 do not  
21 disclose or suggest these elements at least because they do not disclose or suggest administration  
22 of EPA with the recited purity to a subject with the recited very high TG levels. The cited

23 \_\_\_\_\_  
24 <sup>3299</sup> AstraZeneca AB v. Dr. Reddy’s Labs., Ltd., No. CIV.A.05-5553 JAP, 2010 WL 1981790, at \*11–12 (D.N.J.  
May 18, 2010).

1 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition  
2 with the recited fatty acid compositions or dosage.

3 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
4 WO '118 does not disclose or suggest a subject with the recited very high TG level. WO '118  
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
6 acid composition or dosage. With respect to claim 1, the cited portions of WO '118 further do  
7 not disclose or suggest a method to effect the recited TG reduction without substantially  
8 increasing LDL-C. With respect to claim 10, the cited portions of WO '118 further do not  
9 disclose or suggest a method that is effective to reduce the recited very high TG levels without  
10 substantially increasing LDL-C in a first patient population with the recited very high TG levels  
11 receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a  
12 comparison to a second patient population with the recited very high TG levels who has not  
13 received the pharmaceutical composition.

14 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
15 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
16 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first  
17 patient population with the claimed TG level. With respect to Claims 8 and 17, this reference  
18 fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient  
19 population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to  
20 disclose or suggest the recited reduction in VLDL-C in the subject or first patient population  
21 with the claimed TG level.

22 (2) WO '900

23 WO '900 describes methods for obtaining EPA-rich compositions.  
24

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
2 '900 disclose or suggest elements of the '652 Claims. The cited portions of WO '900 do not  
3 disclose or suggest these elements at least because they do not disclose or suggest administration  
4 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
5 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition  
6 with the recited fatty acid dosage or administration period.

7 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
8 WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900  
9 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
10 acid dosage or administration period. With respect to claim 1, the cited portions of WO '900  
11 further do not disclose or suggest a method to effect the recited TG reduction without  
12 substantially increasing LDL-C. With respect to claim 10, the cited portions of WO '900 further  
13 do not disclose or suggest a method that is effective to reduce the recited very high TG levels  
14 without substantially increasing LDL-C in a first patient population with the recited very high  
15 TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition,  
16 based on a comparison to a second patient population with the recited very high TG levels who  
17 has not received the pharmaceutical composition.

18 Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
19 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this  
20 reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
21 respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and  
22 LDL-C effects in the subject or first patient population with the claimed TG level. With respect  
23 to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in  
24

1 Apolipoprotein B in the subject or first patient population with the claimed TG level. With  
2 respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in  
3 VLDL-C in the subject or first patient population with the claimed TG level.

4 (3) Contacos

5 Contacos describes a study designed to determine the safety and efficacy of a statin  
6 (pravastatin) combined with fish oil either alone or in combination, for the management of  
7 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in  
8 the claims.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
10 Contacos disclose or suggest elements of the '652 Claims. The cited portions of Contacos do not  
11 disclose or suggest these elements at least because they do not disclose or suggest administration  
12 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
13 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition  
14 with the recited fatty acid compositions, dosage or administration period.

15 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
16 Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos  
17 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
18 acid compositions, dosage, or administration period. With respect to claim 1, the cited portions  
19 of Contacos further do not disclose or suggest a method of administering the claimed  
20 pharmaceutical composition to effect the recited TG reduction without substantially increasing  
21 LDL-C. With respect to claim 10, the cited portions of Contacos further do not disclose or  
22 suggest a method of administering the claimed pharmaceutical composition that is effective to  
23 reduce the recited very high TG levels without substantially increasing LDL-C in a first patient  
24 population with the recited very high TG levels receiving the recited fatty acid dosage of the

1 recited pharmaceutical composition, based on a comparison to a second patient population with  
2 the recited very high TG levels who has not received the pharmaceutical composition.

3 Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
4 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this  
5 reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
6 respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of  
7 the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With  
8 respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the  
9 claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With  
10 respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the  
11 claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

12 (4) Grimsgaard

13 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design  
14 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,  
15 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG  
16 levels.

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
18 Grimsgaard disclose or suggest elements of the '652 Claims. The cited portions of Grimsgaard  
19 do not disclose or suggest these elements at least because they do not disclose or suggest  
20 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
21 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical  
22 composition with the recited fatty acid compositions or administration period.

23 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
24 Grimsgaard does not disclose or suggest a subject with the recited very high TG level.

1 Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the  
2 recited fatty acid composition or administration period. With respect to claim 1, the cited  
3 portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG  
4 reduction without substantially increasing LDL-C in the subject with the claimed TG level. With  
5 respect to claim 10, the cited portions of Grimsgaard further do not disclose or suggest a method  
6 that is effective to reduce the recited very high TG levels without substantially increasing LDL-C  
7 in a first patient population with the recited very high TG levels receiving the recited fatty acid  
8 dosage of the recited pharmaceutical composition, based on a comparison to a second patient  
9 population with the recited very high TG levels who has not received the pharmaceutical  
10 composition.

11 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
12 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
13 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first  
14 patient population with the claimed TG level. With respect to Claims 8 and 17, this reference  
15 fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient  
16 population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to  
17 disclose or suggest the recited reduction in VLDL-C in the subject or first patient population  
18 with the claimed TG level.

19 (5) Hayashi

20 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for  
21 8 weeks. The purity of the composition is not reported. The study was not placebo controlled  
22 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride  
23 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220  
24 mg/dl.

1 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the  
2 '652 patent claims. For example, the cited portions of Hayashi do not disclose or suggest  
3 administration of EPA with the recited purity to a subject with the recited very high TG levels  
4 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject  
5 had a TG level above 400 mg/dl. The cited portions of Hayashi further do not disclose or  
6 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or  
7 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the  
8 recited TG reduction without substantially increasing LDL-C in a subject with the recited very  
9 high TG levels.

10 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
11 Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also  
12 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
13 compositions or dosage. With respect to claim 1, the cited portions of Hayashi further do not  
14 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
15 LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of  
16 Hayashi further do not disclose or suggest a method that is effective to reduce the recited very  
17 high TG levels without substantially increasing LDL-C in a first patient population with the  
18 recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical  
19 composition, based on a comparison to a second patient population with the recited very high TG  
20 levels who has not received the pharmaceutical composition.

21 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
22 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
23 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
24

1 | claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the  
2 | recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
3 | Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
4 | the subject with the claimed TG level.

5 | (6) Katayama

6 | Katayama was directed to an investigation of the safety and efficacy of Epadel during  
7 | long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,  
8 | Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and  
9 | was not placebo controlled.

10 | In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
11 | Katayama disclose or suggest elements of the '652 Claims. The cited portions of Katayama do  
12 | not disclose or suggest these elements at least because they do not disclose or suggest  
13 | administration of EPA with the recited purity to a subject with the recited very high TG levels.  
14 | The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical  
15 | composition with the recited fatty acid compositions or dosage.

16 | With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
17 | Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama  
18 | also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
19 | acid compositions or dosage. With respect to claim 1, the cited portions of Katayama further do  
20 | not disclose or suggest a method to effect the recited TG reduction without substantially  
21 | increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited  
22 | portions of Katayama further do not disclose or suggest a method that is effective to reduce the  
23 | recited very high TG levels without substantially increasing LDL-C in a first patient population  
24 | with the recited very high TG levels receiving the recited fatty acid dosage of the recited



1 pharmaceutical composition, based on a comparison to a second patient population with the  
2 recited very high TG levels who has not received the pharmaceutical composition.

3 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
4 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
5 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
6 claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the  
7 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
8 Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
9 the subject with the claimed TG level.

10 (7) Leigh-Firbank

11 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle  
12 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank  
13 does not administer EPA of the purity recited in the claims.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
15 Leigh-Firbank disclose or suggest elements of the '652 Claims. The cited portions of Leigh-  
16 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest  
17 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
18 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed  
19 pharmaceutical composition with the recited fatty acid compositions, dosage or administration  
20 period.

21 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
22 Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-  
23 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the  
24 recited fatty acid compositions, dosage, or administration period. With respect to claim 1, the

1 | cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the  
2 | claimed pharmaceutical composition to effect the recited TG reduction without substantially  
3 | increasing LDL-C. With respect to claim 10, the cited portions of Leigh-Firbank further do not  
4 | disclose or suggest a method of administering the claimed pharmaceutical composition that is  
5 | effective to reduce the recited very high TG levels without substantially increasing LDL-C in a  
6 | first patient population with the recited very high TG levels receiving the recited fatty acid  
7 | dosage of the recited pharmaceutical composition, based on a comparison to a second patient  
8 | population with the recited very high TG levels who has not received the pharmaceutical  
9 | composition.

10 | Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
11 | administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this  
12 | reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
13 | respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of  
14 | the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With  
15 | respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the  
16 | claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With  
17 | respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the  
18 | claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

19 | (8) Lovaza PDR

20 | The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

21 | In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
22 | Lovaza PDR disclose or suggest elements of the '652 Claims. The cited portions of the Lovaza  
23 | PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
24 | administration of EPA with the recited purity to a subject with the recited very high TG levels.

1 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed  
2 pharmaceutical composition with the recited fatty acid compositions or administration period.

3 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), the  
4 Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the  
5 recited fatty acid compositions or administration period. With respect to claim 1, the cited  
6 portions of the Lovaza PDR further do not disclose or suggest a method of administering the  
7 claimed pharmaceutical composition to effect the recited TG reduction without substantially  
8 increasing LDL-C. With respect to claim 10, the cited portions of the Lovaza PDR further do  
9 not disclose or suggest a method of administering the claimed pharmaceutical composition that is  
10 effective to reduce the recited very high TG levels without substantially increasing LDL-C in a  
11 first patient population with the recited very high TG levels receiving the recited fatty acid  
12 dosage of the recited pharmaceutical composition, based on a comparison to a second patient  
13 population with the recited very high TG levels who has not received the pharmaceutical  
14 composition.

15 Further, with respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest  
16 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
17 C effects. With respect to Claims 8 and 17, this reference fails to disclose or suggest the  
18 administration of the claimed pharmaceutical composition to effect the recited reduction in  
19 Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the  
20 administration of the claimed pharmaceutical composition to effect the recited reduction in  
21 VLDL-C.

22 (9) Maki

23 Maki administered 1.52g/day DHA supplements to patients with below-average levels of  
24 HDL-C. Maki does not administer EPA of the purity recited in the claims.

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki  
2 disclose or suggest elements of the '652 Claims. The cited portions of Maki do not disclose or  
3 suggest these elements at least because they do not disclose or suggest administration of EPA  
4 with the recited purity to a subject with the recited very high TG levels. The cited portions of  
5 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited  
6 fatty acid compositions, dosage or administration period.

7 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
8 Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does  
9 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
10 compositions, dosage, or administration period. With respect to claim 1, the cited portions of  
11 Maki further do not disclose or suggest a method of administering the claimed pharmaceutical  
12 composition to effect the recited TG reduction without substantially increasing LDL-C. With  
13 respect to claim 10, the cited portions of Maki further do not disclose or suggest a method of  
14 administering the claimed pharmaceutical composition that is effective to reduce the recited very  
15 high TG levels without substantially increasing LDL-C in a first patient population with the  
16 recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical  
17 composition, based on a comparison to a second patient population with the recited very high TG  
18 levels who has not received the pharmaceutical composition.

19 Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
20 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this  
21 reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
22 respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of  
23 the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With  
24

1 | respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the  
2 | claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With  
3 | respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the  
4 | claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

5 | (10) Matsuzawa

6 | Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-  
7 | term use in the treatment of the disease and was not placebo controlled.

8 | In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
9 | Matsuzawa disclose or suggest elements of the '652 Claims. The cited portions of Matsuzawa  
10 | do not disclose or suggest these elements at least because they do not disclose or suggest  
11 | administration of EPA with the recited purity to a subject with the recited very high TG levels.  
12 | The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical  
13 | composition with the recited fatty acid compositions or dosage.

14 | With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
15 | Matsuzawa does not disclose or suggest a subject with the recited very high TG level.  
16 | Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the  
17 | recited fatty acid compositions or dosage. With respect to claim 1, the cited portions of  
18 | Matsuzawa further do not disclose or suggest a method of administering the claimed  
19 | pharmaceutical composition to effect the recited TG reduction without substantially increasing  
20 | LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of  
21 | Matsuzawa further do not disclose or suggest a method of administering the claimed  
22 | pharmaceutical composition to reduce the recited very high TG levels without substantially  
23 | increasing LDL-C in a first patient population with the recited very high TG levels receiving the  
24 | recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a

1 second patient population with the recited very high TG levels who has not received the  
2 pharmaceutical composition.

3 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
4 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
5 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
6 composition to effect the recited TG and LDL-C effects in the subject with the claimed TG level.  
7 With respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of  
8 the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in  
9 the subject with the claimed TG level. With respect to Claims 9 and 18, this reference fails to  
10 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
11 recited reduction in VLDL-C in the subject with the claimed TG level.

12 (11) Mori 2000

13 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum  
14 lipids and lipoproteins, glucose and insulin in humans.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
16 2000 disclose or suggest elements of the '652 Claims. The cited portions of Mori 2000 do not  
17 disclose or suggest these elements at least because they do not disclose or suggest administration  
18 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
19 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition  
20 with the recited fatty acid compositions or administration period.

21 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
22 Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000  
23 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
24 acid composition or administration period. With respect to claim 1, the cited portions of Mori

1 2000 further do not disclose or suggest a method to effect the recited TG reduction without  
2 substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim  
3 10, the cited portions of Mori 2000 further do not disclose or suggest a method that is effective to  
4 reduce the recited very high TG levels without substantially increasing LDL-C in a first patient  
5 population with the recited very high TG levels receiving the recited fatty acid dosage of the  
6 recited pharmaceutical composition, based on a comparison to a second patient population with  
7 the recited very high TG levels who has not received the pharmaceutical composition.

8 Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
9 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this  
10 reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
11 respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and  
12 LDL-C effects in the subject or first patient population with the claimed TG level. With respect  
13 to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in  
14 Apolipoprotein B in the subject or first patient population with the claimed TG level. With  
15 respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in  
16 VLDL-C in the subject or first patient population with the claimed TG level.

17 (12) Mori 2006

18 Mori 2006 is a review which reports data from clinical trials which compared the  
19 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

20 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
21 2006 disclose or suggest elements of the '652 Claims. The cited portions of Mori 2006 do not  
22 disclose or suggest these elements at least because they do not disclose or suggest administration  
23 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
24

1 portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition  
2 with the recited fatty acid dosage or administration period.

3 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
4 Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006  
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
6 acid dosage or administration period. With respect to claim 1, the cited portions of Mori 2006  
7 further do not disclose or suggest a method to effect the recited TG reduction without  
8 substantially increasing LDL-C. With respect to claim 10, the cited portions of Mori 2006  
9 further do not disclose or suggest a method that is effective to reduce the recited very high TG  
10 levels without substantially increasing LDL-C in a first patient population with the recited very  
11 high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition,  
12 based on a comparison to a second patient population with the recited very high TG levels who  
13 has not received the pharmaceutical composition.

14 Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
15 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this  
16 reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
17 respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and  
18 LDL-C effects in the subject or first patient population with the claimed TG level. With respect  
19 to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in  
20 Apolipoprotein B in the subject or first patient population with the claimed TG level. With  
21 respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in  
22 VLDL-C in the subject or first patient population with the claimed TG level.



1 (13) Nozaki

2 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The  
3 purity of the composition is reported as 90%. The study was not placebo controlled and was  
4 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165  
5 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG  
6 patient population.

7 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the  
8 '652 patent claims. For example, the cited portions of Nozaki do not disclose or suggest  
9 administration of EPA with the recited purity to a subject with the recited very high TG levels  
10 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do  
11 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
12 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a  
13 method to effect the recited TG reduction without substantially increasing LDL-C in a subject  
14 with the recited very high TG levels.

15 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the  
16 '652 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least  
17 because they do not disclose or suggest administration of EPA with the recited purity to a subject  
18 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The  
19 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical  
20 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki  
21 further do not disclose or suggest a method to effect the recited TG reduction without  
22 substantially increasing LDL-C.

23 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
24 Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also

1 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions or dosage. With respect to claim 1, the cited portions of Nozaki further do not  
3 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
4 LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of  
5 Nozaki further do not disclose or suggest a method that is effective to reduce the recited very  
6 high TG levels without substantially increasing LDL-C in a first patient population with the  
7 recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical  
8 composition, based on a comparison to a second patient population with the recited very high TG  
9 levels who has not received the pharmaceutical composition.

10 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
11 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
12 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
13 claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the  
14 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
15 Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
16 the subject with the claimed TG level.

17 (14) Omacor PDR

18 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
20 Omacor PDR disclose or suggest elements of the '652 Claims. The cited portions of the Omacor  
21 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
22 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
23 The cited portions of the Omacor PDR further do not disclose or suggest the claimed  
24 pharmaceutical composition with the recited fatty acid compositions or administration period.

1 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), the  
2 Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the  
3 recited fatty acid compositions or administration period. With respect to claim 1, the cited  
4 portions of the Omacor PDR further do not disclose or suggest a method of administering the  
5 claimed pharmaceutical composition to effect the recited TG reduction without substantially  
6 increasing LDL-C. With respect to claim 10, the cited portions of the Omacor PDR further do  
7 not disclose or suggest a method of administering the claimed pharmaceutical composition that is  
8 effective to reduce the recited very high TG levels without substantially increasing LDL-C in a  
9 first patient population with the recited very high TG levels receiving the recited fatty acid  
10 dosage of the recited pharmaceutical composition, based on a comparison to a second patient  
11 population with the recited very high TG levels who has not received the pharmaceutical  
12 composition.

13 Further, with respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest  
14 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
15 C effects. With respect to Claims 8 and 17, this reference fails to disclose or suggest the  
16 administration of the claimed pharmaceutical composition to effect the recited reduction in  
17 Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the  
18 administration of the claimed pharmaceutical composition to effect the recited reduction in  
19 VLDL-C.

20 (15) Satoh

21 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
22 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
23 systemic inflammation.

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
2 Satoh disclose or suggest elements of the '652 Claims. The cited portions of Satoh do not  
3 disclose or suggest these elements at least because they do not disclose or suggest administration  
4 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
5 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with  
6 the recited fatty acid compositions or dosage.

7 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
8 Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does  
9 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
10 composition or dosage. With respect to claim 1, the cited portions of Satoh further do not  
11 disclose or suggest a method to effect the recited TG reduction without substantially increasing  
12 LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of  
13 Satoh further do not disclose or suggest a method that is effective to reduce the recited very high  
14 TG levels without substantially increasing LDL-C in a first patient population with the recited  
15 very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical  
16 composition, based on a comparison to a second patient population with the recited very high TG  
17 levels who has not received the pharmaceutical composition.

18 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
19 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
20 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first  
21 patient population with the claimed TG level. With respect to Claims 8 and 17, this reference  
22 fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient  
23 population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to  
24

1 disclose or suggest the recited reduction in VLDL-C in the subject or first patient population  
2 with the claimed TG level.

3 (16) Shinozaki

4 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and  
5 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
7 Shinozaki disclose or suggest elements of the '652 Claims. The cited portions of Shinozaki do  
8 not disclose or suggest these elements at least because they do not disclose or suggest  
9 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
10 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical  
11 composition with the recited fatty acid dosage.

12 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
13 Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki  
14 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
15 acid dosage. With respect to claim 1, the cited portions of Shinozaki further do not disclose or  
16 suggest a method to effect the recited TG reduction without substantially increasing LDL-C in  
17 the subject with the claimed TG level. With respect to claim 10, the cited portions of Shinozaki  
18 further do not disclose or suggest a method that is effective to reduce the recited very high TG  
19 levels without substantially increasing LDL-C in a first patient population with the recited very  
20 high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition,  
21 based on a comparison to a second patient population with the recited very high TG levels who  
22 has not received the pharmaceutical composition.

23 Further, with respect to Claims 2 and 11, this reference does not disclose or suggest  
24 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this

1 reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With  
2 respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and  
3 LDL-C effects in the subject or first patient population with the claimed TG level. With respect  
4 to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in  
5 Apolipoprotein B in the subject or first patient population with the claimed TG level. With  
6 respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in  
7 VLDL-C in the subject or first patient population with the claimed TG level.

8 (17) Takaku

9 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-  
10 term use and was not placebo controlled.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
12 Takaku disclose or suggest elements of the '652 Claims. The cited portions of Takaku do not  
13 disclose or suggest these elements at least because they do not disclose or suggest administration  
14 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
15 portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition  
16 with the recited fatty acid compositions or dosage.

17 With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims),  
18 Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also  
19 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
20 compositions or dosage. With respect to claim 1, the cited portions of Takaku further do not  
21 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
22 the recited TG reduction without substantially increasing LDL-C in the subject with the claimed  
23 TG level. With respect to claim 10, the cited portions of Takaku further do not disclose or  
24 suggest a method of administering the claimed pharmaceutical composition to reduce the recited

1 very high TG levels without substantially increasing LDL-C in a first patient population with the  
2 recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical  
3 composition, based on a comparison to a second patient population with the recited very high TG  
4 levels who has not received the pharmaceutical composition.

5 Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the  
6 subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this  
7 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first  
8 patient population with the claimed TG level. With respect to Claims 8 and 17, this reference  
9 fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient  
10 population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to  
11 disclose or suggest the recited reduction in VLDL-C in the subject or first patient population  
12 with the claimed TG level.

13 c) The Prior Art Does Not Render the Claims Obvious

14 Defendants have not identified by clear and convincing evidence that the asserted claims  
15 of the '652 Patent would have been *prima facie* obvious in light of the references cited, either  
16 alone or in combination. As described above, none of the references discloses all of the elements  
17 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without  
18 explanation, and argue they somehow must be combined to render obvious the asserted claims.  
19 Where Defendants have failed to make disclosures with the specificity required by Local Patent  
20 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the  
21 claim elements at issue.

22 Defendants' contentions fail to disclose each and every element of the claims of the '652  
23 patent. Specifically, Defendants do not contend that the relied upon references disclose the  
24 following elements of Claim 10 (and therefore Claims 11-18): a pharmaceutical composition,

1 which when orally administered in a first patient population having said baseline triglyceride  
2 level and receiving, for a period of twelve weeks, 4 g per day of the pharmaceutical composition,  
3 is effective to reduce said baseline triglyceride level without substantially increasing LDL-C,  
4 based upon a comparison to a second patient population having said baseline triglyceride level  
5 that has not received the pharmaceutical composition. Therefore, Defendants' prior art  
6 combinations cannot render the claims *prima facie* obvious.

7 Facts supporting the non-obviousness of the claims of the '652 patent are discussed in  
8 detail below. The objective indicia discussed in Section V.O further demonstrate that the '652  
9 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims  
10 would have been obvious.

11 (1) Defendants Do Not Demonstrate that the Independent  
12 Claims of the '652 Patent Would Have Been Obvious

13 (a) Defendants Do Not Demonstrate that a Person of  
14 Ordinary Skill in the Art Would Have Had Any  
Reason to Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with Pure EPA

15 (i) The '652 Patent is not Obvious Over the  
16 Omacor PDR/Lovaza PDR, in Combination  
17 with Katayama and/or Matsuzawa, Further  
in View of Nozaki and/or Hayashi and  
Further in View of Leigh-Firbank and/or  
Mori 2000

18 With respect to the '652 Patent, Defendants present a combination of seven references:  
19 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering  
20 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or  
21 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000."<sup>3300</sup> Defendants also present  
22

23  
24 <sup>3300</sup> Defendants' Joint Invalidity Contentions at 349.



1 charts purporting to assert that an additional 61 references may be combined in order to render  
2 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary  
3 skill would combine 61 separate references, they additionally do not identify any motivation for  
4 combining these references.<sup>3301, 3302</sup> Although Defendants need not point to an explicit statement  
5 in the prior art motivating the combination of these references, any assertion of an “apparent  
6 reason” to combine must find a basis in the factual record.<sup>3303</sup> Defendants’ unsupported cobbling  
7 of selective disclosures represents hindsight reconstruction.<sup>3304</sup> Defendants’ contentions are no  
8  
9

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10 <sup>3301</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as  
11 described in the references cited above in section V.B.2) in view of, at least, the references cited in V.B.3 and 4,  
12 including, the ‘954 publication, WO ‘900, WO ‘118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataka,  
13 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,  
14 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006,  
15 Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent  
16 Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity  
17 Contentions at 349.

18 <sup>3302</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
19 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
20 and that “[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person  
21 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
22 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 347-48.

24 <sup>3303</sup> *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi  
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3304</sup> *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 more than an assertion that certain claim elements were known in the prior art. Throughout their  
2 contentions, Defendants’ selectively cite to data points in a reference without considering other  
3 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
4 that it teaches.<sup>3305</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
5 obviousness.

6 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
7 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed  
8 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a  
9 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the  
10 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a  
11 significant increase in LDL-C levels in the very high TG patient population, for whom the  
12 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,  
13 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce  
14 TG levels in adult patients with very-high ( $\geq 500$  mg/dL) TG levels.

15 The proposed combinations do not render the independent claims of the ’652 Patent  
16 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
17 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza  
18 package insert specifically) during prosecution.<sup>3306</sup>

19 The analysis of the independent claims of the ’652 Patent are incorporated into all  
20 asserted claims that depend from those Claims.

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22 <sup>3305</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>3306</sup> *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 (a) A Person of Ordinary Skill Would  
2 Not Have Been Motivated to  
3 Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with Pure EPA

4 For an invention to be obvious, there must have been an “apparent reason” to make it.  
5 The subject matter of the ‘652 patent claims would not have been obvious in light of these  
6 references because a person of ordinary skill would not have been motivated to purify EPA or  
7 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
8 levels without an increase in LDL-C levels.

9 (i) Katayama and/or Matsuzawa  
10 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

11 Both Katayama and Matsuzawa are long term studies directed to an investigation of the  
12 safety and efficacy of Epedel in patients with a wide range of baseline TG levels. These studies  
13 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may  
14 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the  
15 art would not and could not attribute any observed effect (and the magnitude of that effect) to  
16 that of the drug. Any observed effect could be placebo dependent.<sup>3307</sup> As discussed above in  
17 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with  
18 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG  
19 patients because patients with higher TG levels had different lipid responses compared to  
20 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally  
21 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical

22 \_\_\_\_\_  
23 <sup>3307</sup>See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a  
24 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a  
placebo-controlled study and why results compared only to baseline may be misleading.)

1 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary  
2 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were  
3 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art  
4 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-  
5 high or high TG patients, was expected. At the priority date of the '652 patent, a person of  
6 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients  
7 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been  
8 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG  
9 lowering through increased VLDL particle conversion.

10 Defendants argue that these studies disclose known “clinical benefits” of administering  
11 pure EPA, lowering triglycerides without raising LDL-C.<sup>3308</sup> This is an incorrect characterization  
12 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of  
13 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.  
14 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.  
15 Defendants’ selective citation of LDL-C data from these references represents the improper use  
16 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and  
17 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw  
18 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C  
19 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the  
20 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.<sup>3309</sup> The  
21 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor  
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23 <sup>3308</sup> Defendants’ Joint Invalidation Contentions at 350.

24 <sup>3309</sup> Defendants’ Joint Invalidation Contentions at 349-50.

1 would a person of ordinary skill view these references as teaching such a benefit for very-high  
2 TG patients.

3 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid  
4 effects. These studies fail to provide a head to head comparison of EPA versus DHA.  
5 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to  
6 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

7 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The  
8 purity of Epadel has varied over time and across different formulations of the product, therefore  
9 it is difficult to determine the purity of the version of Epadel used unless it is specified by the  
10 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the  
11 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and  
12 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference  
13 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

14 Nishikawa,<sup>3310</sup> published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.  
15 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite  
16 purity.<sup>3311</sup>

17 Further, Katayama and Matsuzawa were small studies conducted in only Japanese  
18 patients. These studies would not have been extrapolated to Western populations because the  
19 Japanese diet contains much more fish and has a number of other different attributes. The  
20 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In  
21

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22 <sup>3310</sup> Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS*  
23 *Analysis of PGI<sub>2</sub> and PGI<sub>3</sub> Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 <sup>3311</sup> See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

1 fact, Yokoyama 2007 (cited in Defendants’ contentions) states that the results from studies where  
2 the patient population is exclusively Japanese cannot be generalized to other populations.<sup>3312</sup>  
3 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical  
4 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-  
5 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand  
6 that the Japanese respond differently to lipid lowering agents than Westerners.

7 Defendants rely on Katayama to demonstrate the “known clinical benefits of  
8 administering pure EPA - lowering triglycerides without raising LDL-C.”<sup>3313</sup> However,  
9 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term  
10 treatment in patients with hyperlipidemia.<sup>3314</sup> Katayama does not disclose *any* LDL-C related  
11 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that  
12 reference to provide any such disclosure. The only results disclosed by Katayama were a  
13 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was  
14 administered to patients with borderline-high to high TG levels, and its safety for long term use  
15 in this patient population.<sup>3315</sup> In addition to Katayama’s lack of disclosure regarding LDL-C,  
16 Defendants identify no other basis upon which a person of ordinary skill would have sought to  
17 combine the composition disclosed in Katayama with the Lovaza PDR.

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21 <sup>3312</sup> Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

22 <sup>3313</sup> Defendants’ Joint Invalidity Contentions at 350.

23 <sup>3314</sup> Katayama at 2.

24 <sup>3315</sup> *Id.* at 16.

1 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of  
2 administering pure EPA - lowering triglycerides without raising LDL-C.”<sup>3316</sup> However,  
3 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall  
4 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of  
5 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13  
6 were evaluated for improvement in serum triglycerides levels.<sup>3317</sup> It is unclear which of the 26  
7 patients were included in each separate evaluation; therefore one cannot determine the baseline  
8 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack  
9 of a placebo control makes it less likely that the results of this study can be generalized as an  
10 effect on any population as a whole and provides no insight with respect to the very-high TG  
11 patient population.

12 Matsuzawa discloses that 3 of the 26 participants had  $400 \text{ mg/dL} < \text{TG} < 1000 \text{ mg/dL}$ ,  
13 and one participant with TG levels  $> 1,000 \text{ mg/dL}$ .<sup>3318</sup> However, when analyzing the lipid  
14 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL  
15 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess  
16 triglyceride levels.”<sup>3319</sup> Fig. 4, which depicts the changes in serum triglycerides, shows that the  
17 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500  
18 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than  
19 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of  
20 undisclosed purity). The identification of three patients with TG levels between 400 and less

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22 <sup>3316</sup> Defendants’ Joint Invalidation Contentions at 350.

23 <sup>3317</sup> Matsuzawa at 7 and 19.

24 <sup>3318</sup> *Id.* at 23.

<sup>3319</sup> *Id.* at 10.

1 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of  
2 ordinary skill would not understand that the reference makes any such disclosure. As discussed  
3 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG  
4 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no  
5 evidence to the contrary.

6 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a  
7 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.<sup>3320</sup> The disclosure  
8 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were  
9 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-  
10 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at  
11 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with  
12 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of  
13 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary  
14 skill in the art, however, would have expected the same treatment in patients with very high TG  
15 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that  
16 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered  
17 triglyceride levels.<sup>3321</sup> At best, Matsuzawa demonstrates the uncertainty and confusion related to  
18 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify  
19 any other basis upon which a person of ordinary skill would have sought to combine the  
20 composition disclosed in Matsuzawa with the Lovaza PDR.

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22 <sup>3320</sup> *Id.* at 11.

23 <sup>3321</sup> *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA  
24 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific  
compositions used, or identify the patient populations were observed.



1 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that  
2 compositions comprising EPA as recited in the asserted claims lowers triglycerides without  
3 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA  
4 increases LDL-C.<sup>3322</sup> Defendants identify no other basis upon which a person of ordinary skill  
5 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank  
6 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the  
7 asserted claims of the '652 patent.

8 (ii) Nozaki and/or Hayashi  
9 Would Not Have Rendered  
10 the Asserted Claims Obvious

11 Defendants contend that the asserted claims of the '652 patent would have been obvious  
12 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
13 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
14 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
15 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
16 very high TG patient population.

17 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
18 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
19 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
20 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
21 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
22 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
23 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

24 <sup>3322</sup> See, e.g., Rambjor.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
2 patient population were abnormally high and would not have relied upon these results. Further,  
3 the person of skill in the art would not have looked to this patient population to predict the Apo-  
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
6 levels.<sup>3323</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
12 the EPA and the DHA content in the composition that was administered is unknown. A person  
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
15 C were not statistically significant.<sup>3324</sup> Further, the person of skill in the art would not have  
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
21 administered to the very high TG patient population.

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23 <sup>3323</sup> Nozaki at 256.

24 <sup>3324</sup> Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not  
2 placebo controlled. This study would not have been extrapolated to Western populations  
3 because the Japanese diet contains much more fish and has a number of other different attributes.  
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
5 populations. In fact, Defendants' own reference states that the results from studies where the  
6 patient population is exclusively Japanese cannot be generalized to other populations.<sup>3325</sup> The  
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
10 the Japanese respond differently to lipid lowering agents than Westerners.

11 Further, Defendants have failed to offer a purported combination of references as part of  
12 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
13 motivation to combine Nozaki and Hayashi with the other references of their purported  
14 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
15 references.

16 (iii) Leigh-Firbank and/or Mori  
17 2000 Do Not Disclose  
18 Purported Knowledge that  
19 DHA was Responsible for the  
20 Increase in LDL-C

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that  
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
21 C levels."<sup>3326</sup> Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

22 \_\_\_\_\_  
23 <sup>3325</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
24 other populations.").

<sup>3326</sup> Defendants' Joint Invalidity Contentions at 352.

1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
2 rely upon to support this statement does not categorize the increase in LDL-C as a “negative  
3 effect” in light of the overall impact of the disclosed composition on all lipid parameters.  
4 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As  
5 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
6 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—  
7 as in very-high TG patients because patients with higher TG levels had different lipid responses  
8 compared to patients with lower TG levels. Patients with very-high TG levels were considered  
9 fundamentally different from patients with borderline-high or high triglycerides from a lipid  
10 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person  
11 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)  
12 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but  
13 would substantially increase LDL-C in patients with very high TG levels.

14 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was  
15 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,  
16 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride  
17 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either  
18 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A  
19 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any  
20 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the  
21 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)  
22 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated  
23 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA  
24

1 and DHA.<sup>3327</sup> A person of ordinary skill would understand that studies directed to EPA and  
2 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on  
3 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-  
4 Firbank, because purified EPA and DHA were not administered separately.

5 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent  
6 effects of EPA and DHA individually, even though it administered a combination of EPA and  
7 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions  
8 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet  
9 phospholipid EPA were *independently* associated with the decrease in fasting TGs,<sup>3328</sup> and DHA  
10 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state  
11 of the art and numerous publications cited by Defendants.<sup>3329</sup> It is widely accepted that DHA  
12 also has a hypotriglyceridemic effect.

13 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients  
14 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-  
15 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching  
16 away from the claimed invention. “A reference may be said to teach away when a person of  
17 ordinary skill, upon [examining] the reference, would be discouraged from following the path set  
18 out in the reference, or would be led in a direction divergent from the path that was taken by the  
19 applicant.”<sup>3330</sup> Although teaching away is fact-dependent, “in general, a reference will teach

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21 <sup>3327</sup> Mori 2006 at 96.

22 <sup>3328</sup> Leigh-Firbank at 440.

23 <sup>3329</sup> See, e.g. Grimsgaard at 654.

24 <sup>3330</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

1 away if it suggests that the line of development flowing from the reference’s disclosures is  
2 unlikely to be productive of the result sought by the applicant.”<sup>3331</sup>

3 Mori 2000 concludes that the changes effected by DHA supplementation “may represent  
4 a more favorable lipid profile than after EPA supplementation.”<sup>3332</sup> For example, it states that  
5 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL  
6 cholesterol and a significant increase in the HDL<sub>2</sub>-cholesterol subfraction, without adverse  
7 effects on fasting glucose concentrations.”<sup>3333</sup> Mori 2000 also states that “[d]espite an increase  
8 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may  
9 be favorable.”<sup>3334</sup> Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori  
10 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the  
11 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away  
12 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for  
13 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,  
14 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration  
15 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,  
16 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
17 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill  
18 would have sought to combine Mori 2000 with the Lovaza PDR.

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21 <sup>3331</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354  
(Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)  
(“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

22 <sup>3332</sup> Mori 2000 at 1092.

23 <sup>3333</sup> Mori 2000 at 1088.

24 <sup>3334</sup> Mori 2000 at 1092.



1 factual record.<sup>3337</sup> Defendants’ unsupported cobbling of selective disclosures represents  
2 hindsight reconstruction.<sup>3338</sup> Defendants’ contentions are no more than an assertion that certain  
3 claim elements were known in the prior art. Throughout their contentions, Defendants’  
4 selectively cite to data points in a reference without considering other disclosures or even the  
5 reference as a whole. Each reference, however, must be evaluated for all that it teaches.<sup>3339</sup>  
6 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

7         The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method  
8 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the  
9 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR  
10 further do not disclose a method to effect the claimed TG reduction without substantially  
11 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA  
12 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the  
13 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose  
14 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375  
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16 <sup>3337</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3338</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>3339</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011).



1 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500  
2 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '652  
3 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the  
4 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both  
5 generally and the Lovaza package insert specifically) during prosecution.<sup>3340</sup>

6 The analysis of the independent claims of the '652 Patent are incorporated into all  
7 asserted claims that depend from those Claims.

8 (a) A Person of Ordinary Skill Would  
9 Not Have Been Motivated to  
10 Replace the Mixed Fish Oil Active  
Ingredient in Omacor/Lovaza with  
EPA of the Claimed Purity

11 For an invention to be obvious, there must have been an "apparent reason" to make it.  
12 The subject matter of the '652 patent claims would not have been obvious in light of these  
13 references because a person of ordinary skill would not have been motivated to purify EPA or  
14 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
15 levels without an increase in LDL-C levels.

16 (i) Grimsgaard, Katayama,  
17 Matsuzawa and/or Takaku  
18 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

19 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the  
20 "known clinical benefits of administering pure EPA - lowering triglycerides without raising  
21 LDL-C." As discussed in Section V.G.3.c.1.a.i.a.i, incorporated herein by reference, Katayama

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23 <sup>3340</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").

1 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to  
2 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported  
3 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that  
4 the LDL-C results obtained were a clinical benefit.

5 Defendants also rely on Grimsgaard to support their assertion that “administration of  
6 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”<sup>3341</sup> However,  
7 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on  
8 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

9 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA  
10 administered to people with normal triglyceride levels for 7 weeks.<sup>3342</sup> The results from the  
11 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the  
12 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that  
13 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid  
14 supplements, which is consistent with previous studies which “suggested that serum HDL-C is  
15 better maintained with oil rich in DHA than oil rich in EPA.”<sup>3343</sup> Although Grimsgaard states  
16 that EPA may produce a small decrease in serum total cholesterol, it does not specifically  
17 comment on EPA’s effect on LDL-C.

18 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to  
19 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in  
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21 <sup>3341</sup> Defendants’ Joint Invalidity Contentions at 353.

22 <sup>3342</sup> Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG  
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG  
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

<sup>3343</sup> Grimsgaard at 654.

LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”<sup>3344</sup> The results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants’ Joint Invalidity Contentions.

TABLE 4  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test; P <sup>f</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>2</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
<b>LDL cholesterol (mmol/L)</b>	<b>4.06 ± 0.86</b>	<b>0.07 ± 0.46</b>	<b>4.06 ± 0.83</b>	<b>-0.08 ± 0.48</b>	<b>4.04 ± 0.98</b>	<b>0.06 ± 0.48</b>	<b>0.10</b>	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>3</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>3</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>5</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>3</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>3</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>4</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>5</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>f</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>3-5</sup> One-sample t test of difference between baseline and 7 wk: <sup>3</sup> P < 0.001, <sup>4</sup> P < 0.01, <sup>5</sup> P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”<sup>3345</sup> However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of

<sup>3344</sup> Defendants’ Joint Invalidity Contentions at 352 n.53.

<sup>3345</sup> Grimsgaard at 657.

1 patients with very-high triglycerides, because net decrease in triglycerides was consistently  
2 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared  
3 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL  
4 cholesterol observed with some n-3 fatty acid supplements.”<sup>3346</sup> Grimsgaard makes no such  
5 statement regarding LDL-C.

6 Defendants cherry-pick results, regardless of whether the effect is found to be statistically  
7 significant compared to placebo, in an attempt to force the studies to support their argument that  
8 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did  
9 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and  
10 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and  
11 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified  
12 DHA results in increased LDL-C levels while administration of purified EPA resulted in a  
13 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did  
14 not have statistically significantly effects on LDL-C compared to placebo.<sup>3347</sup> A person of  
15 ordinary skill would not draw conclusions regarding differences between EPA and DHA based  
16 on statistically insignificant results.

17 Defendants also rely on Takaku to support their assertion that “clinical benefits of  
18 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the  
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20 <sup>3346</sup> Grimsgaard at 654.

21 <sup>3347</sup>In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a  
22 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to  
23 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have  
24 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make  
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or  
no impact on LDL-C levels.

1 art.<sup>3348</sup> Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and  
2 safety of Epadel (of undisclosed purity)<sup>3349</sup> based on long-term administration.<sup>3350</sup>

3 A person of ordinary skill would not have concluded based on Takaku that EPA lowers  
4 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly  
5 acknowledges that “only a few subjects were examined” and cautions against drawing a  
6 conclusion “only from the results of the present study.”<sup>3351</sup> Because the study did not include  
7 any placebo control, a person of ordinary skill in the art would understand these reports do not  
8 provide the ability to conclude that the observed lipid effects would have occurred independent  
9 of the drug that is administered. In addition, the study was conducted exclusively in Japanese  
10 patients, and a person of ordinary skill would not have expected the results to be applicable to the  
11 general population.<sup>3352</sup>

12 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a  
13 person of ordinary skill would not have expected the results to be applicable to patients with  
14 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because  
15 measurement was not feasible due to “insufficient sample.”<sup>3353</sup> It is possible that patients with  
16 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in  
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<sup>3348</sup> Defendants’ Joint Invalidity Contentions at 350.

19 <sup>3349</sup> It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by  
20 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),  
Nakamura at 23 (Epadel with purity > 90%).

21 <sup>3350</sup> Takaku at ICOSAPENT\_DFNDT00006834.

22 <sup>3351</sup> Takaku at ICOSAPENT\_DFNDT00006897.

23 <sup>3352</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.”)

24 <sup>3353</sup> Takaku at ICOSAPENT\_DFNDT00006884.

1 calculating LDL-C levels when triglyceride level is above 400 mg/dL.<sup>3354</sup> Moreover, the study  
2 does not provide different LDL-C graphs based on the baseline triglyceride levels.<sup>3355</sup> Therefore,  
3 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had  
4 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C  
5 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile  
6 throughout the study period, decreasing slightly at times but increasing by more than 8% at other  
7 times.<sup>3356</sup> Because of this volatility, a person of ordinary skill would not be able to conclude  
8 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in  
9 LDL-C, stating only that the fluctuation in LDL-C was not significant.<sup>3357</sup>

10 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA  
11 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has  
12 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the  
13 administration of *fish oil* to hypercholesterolemia patients.”<sup>3358</sup> In contrast, Takaku states merely  
14 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary  
15 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study  
16 was attributable to fish oil in general, not EPA specifically.

17 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate  
18 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other  
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21 <sup>3354</sup> See Matsuzawa at ICOSPENT\_DFNDTS00006450.  
22 <sup>3355</sup> Takaku at Fig. 13, ICOSAPENT\_DFNDT00006882.  
23 <sup>3356</sup> Takaku at Fig. 14, ICOSAPENT\_DFNDT00006883.  
24 <sup>3357</sup> Takaku at ICOSAPENT\_DFNDT00006897.  
<sup>3358</sup> Takaku at ICOSAPENT\_DFNDT00006897.

1 studies cited by Defendants suggest that EPA increases LDL-C.<sup>3359</sup> Defendants identify no other  
2 basis upon which a person of ordinary skill would have sought to combine the Omacor  
3 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

4 (ii) Nozaki and/or Hayashi  
5 Would Not Have Rendered  
6 the Asserted Claims Obvious

7 Defendants contend that the asserted claims of the '652 patent would have been obvious  
8 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
9 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
10 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
11 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
12 very high TG patient population.

13 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
14 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
15 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
16 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
17 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
18 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
19 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
20 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
21 patient population were abnormally high and would not have relied upon these results. Further,  
22 the person of skill in the art would not have looked to this patient population to predict the Apo-

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23 <sup>3359</sup> See, e.g., Rambjor.  
24

1 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
2 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
3 levels.<sup>3360</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
4 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
5 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
6 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
7 to the very high TG patient population.

8 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
9 the EPA and the DHA content in the composition that was administered is unknown. A person  
10 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
11 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
12 C were not statistically significant.<sup>3361</sup> Further, the person of skill in the art would not have  
13 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
14 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
15 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
16 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
17 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
18 administered to the very high TG patient population.

19 Further, Hayashi was a small study conducted in only Japanese patients and was not  
20 placebo controlled. This study would not have been extrapolated to Western populations  
21 because the Japanese diet contains much more fish and has a number of other different attributes.

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23 <sup>3360</sup> Nozaki at 256.

24 <sup>3361</sup> Hayashi at 26, Table I.



1 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
2 populations. In fact, Defendants' own reference states that the results from studies where the  
3 patient population is exclusively Japanese cannot be generalized to other populations.<sup>3362</sup> The  
4 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
5 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
7 the Japanese respond differently to lipid lowering agents than Westerners.

8 Further, Defendants have failed to offer a purported combination of references as part of  
9 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
10 motivation to combine Nozaki and Hayashi with the other references of their purported  
11 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
12 references.

13 (iii) Grimsgaard, Mori 2000  
14 and/or Maki Do Not Disclose  
15 Purported Knowledge that  
16 DHA was Responsible for the  
17 Increase in LDL-C

18 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that  
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
20 C levels."<sup>3363</sup> Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*  
21 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
22 rely on to support this statement does not categorize the increase in LDL-C as a "negative effect"  
23 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the

23 <sup>3362</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

24 <sup>3363</sup> Defendants' Joint Invalidity Contentions at 352.

1 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.  
2 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
3 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or  
4 Maki—as in very-high TG patients because patients with higher TG levels had different lipid  
5 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
6 considered fundamentally different from patients with borderline-high or high triglycerides from  
7 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of  
8 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would  
9 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would  
10 substantially increase LDL-C in patients with very high TG levels.

11 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known  
12 that “DHA was responsible for the increase in LDL-C levels.”<sup>3364</sup> The discussion related to  
13 Grimsgaard in Section V.G.3.c.1.a.ii.a.i and Mori 2000 in Section V.G.3.c.1.a.i.a.iii is  
14 incorporated herein by reference.

15 Defendants argue that Maki discloses the administration of purified DHA resulted in the  
16 desired reduction of TGs, but also significantly increased LDL-C levels.<sup>3365</sup> Maki was designed  
17 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with  
18 below-average levels of HDL-C levels.<sup>3366</sup> The DHA supplemented group was administered  
19 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,  
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22 <sup>3364</sup> Defendants’ Joint Invalidity Contentions at 350.

23 <sup>3365</sup> Defendants’ Joint Invalidity Contentions at 352.

24 <sup>3366</sup> Maki at 190.

1 monounsaturated and polyunsaturated fatty acids.<sup>3367</sup> Therefore, Maki demonstrated that when  
2 1.52 g/day DHA and 0.84 g/day palmitic acid is administered to patients with below-average  
3 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is  
4 observed.<sup>3368</sup> However, one cannot attribute the rise in LDL-C solely to DHA, because the  
5 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have  
6 also contributed to the elevation in LDL cholesterol.”<sup>3369</sup> Further, Maki admits that the  
7 “mechanism(s) responsible for the changes in the lipid profile associated with DHA  
8 supplementation are not fully understood.”<sup>3370</sup> Therefore, the results of Maki are inconclusive as  
9 to DHA’s effect alone on LDL-C levels.

10 Defendants mischaracterize the rise in LDL-C associated with the administration of  
11 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-  
12 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in  
13 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol  
14 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of  
15 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level  
16 less worrisome.”<sup>3371</sup> Therefore, when one of ordinary skill in the art reviewed all the lipid effects  
17 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was  
18 “less worrisome” because of the “potentially favorable effects on triglycerides, the  
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20 <sup>3367</sup> Maki at 191.

21 <sup>3368</sup> Maki at 195.

22 <sup>3369</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

23 <sup>3370</sup> Maki at 197.

24 <sup>3371</sup> Maki at 197.

1 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense  
2 particles.”<sup>3372</sup>

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
6 has little effect on LDL-C levels.<sup>3373</sup> Defendants identify no other basis upon which a person of  
7 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,  
8 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

9 (iii) The ‘652 Patent is not Obvious Over the  
10 Omacor PDR/Lovaza PDR, in Combination  
11 with Katayama in View of Satoh and/or in  
View of Satoh or Shinozaki in Further View  
of Contacos

12 With respect to the ‘652 Patent, Defendants present a combination of five references: “the  
13 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering  
14 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in  
15 further view of Contacos.”<sup>3374</sup> Defendants also present charts purporting to assert that an  
16 additional 60 references may be combined in order to render the Claims obvious. Not only do  
17 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate  
18 references, they additionally do not suggest any identify for combining these references.  
19 Although Defendants need not point to an explicit statement in the prior art motivating the  
20 combination of these references, any assertion of an “apparent reason” to combine must find a  
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22 <sup>3372</sup> Maki at 197.

23 <sup>3373</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>3374</sup> Defendants’ Joint Invalidity Contentions at 350.

1 basis in the factual record.<sup>3375</sup> Defendants’ unsupported cobbling of selective disclosures  
2 represents hindsight reconstruction.<sup>3376</sup> Defendants’ contentions are no more than an assertion  
3 that certain claim elements were known in the prior art. Throughout their contentions,  
4 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
5 even the reference as a whole. Each reference, however, must be evaluated for all that it  
6 teaches.<sup>3377</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
9 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty  
10 acid compositions or administration period. The Lovaza PDR further does not disclose a method  
11 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza  
12 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference  
13 would cause a significant increase in LDL-C levels in the very high TG patient population, for  
14 whom the product is indicated. At most, the Lovaza PDR discloses administration of a  
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16 <sup>3375</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3376</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>3377</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an  
2 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG  
3 levels.

4 Defendants formulate an obviousness argument that relies on Contacos.<sup>3378</sup> However,  
5 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim  
6 element, an “apparent reason” or motivation to combine the elements in the manner claimed,<sup>3379</sup>  
7 or “a reasonable expectation of success”<sup>3380</sup> of achieving the claimed invention.

8 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and  
9 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,  
10 Contacos fails to provide motivation to administer purified EPA to a very high TG patient  
11 population and does not provide any reasonable expectation of success in lowering TG levels in  
12 the very high TG patient population without increasing LDL-C. Contacos also fails to provide  
13 motivation to administer purified EPA to a very high TG patient population and does not provide  
14 any reasonable expectation of success in lowering TG levels in the very high TG patient  
15 population without increasing LDL-C.

16 The proposed combinations do not render the independent claims of the ’652 Patent  
17 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
18

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19 <sup>3378</sup> *Id.*

20 <sup>3379</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 <sup>3380</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

1 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally  
2 and the Lovaza package insert specifically) during prosecution.<sup>3381</sup>

3 The analysis of the independent claims of the '652 Patent are incorporated into all  
4 asserted claims that depend from those Claims.

5 (a) A Person of Ordinary Skill Would  
6 Not Have Been Motivated to  
7 Replace the Mixed Fish Oil Active  
8 Ingredient in Lovaza with EPA of  
9 the Recited Composition

8 For an invention to be obvious, there must have been an “apparent reason” to make it.  
9 The subject matter of the '652 patent claims would not have been obvious in light of these  
10 references because a person of ordinary skill would not have been motivated to purify EPA or  
11 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
12 levels without an increase in LDL-C levels.

13 (i) Katayama, Satoh and/or  
14 Shinozaki Do Not Disclose  
15 Purported Known Clinical  
16 Benefits of Administering  
17 Pure EPA

16 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical  
17 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As  
18 discussed in Section V.G.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely  
19 confirms the safety of long term treatment of Epadel and its ability to lower both serum total  
20 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone  
21 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or

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22 <sup>3381</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
24 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary  
2 skill view these references as teaching such a benefit for very-high TG patients.

3           Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
4 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
5 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when  
6 compared to baseline, there was no significant effect when compared to placebo.<sup>3382</sup>

7 Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing  
8 LDL-C to be a "clinical benefit" is incorrect.<sup>3383</sup> Satoh does not disclose or suggest that the  
9 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these  
10 references as teaching such a benefit for very-high TG patients. As discussed above, one of  
11 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500  
12 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,  
13 however, would have expected that fish oils (and other TG lowering agents) would substantially  
14 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to  
15 administer purified EPA to a very high TG patient population and does not provide any  
16 reasonable expectation of success in lowering TG levels in the very high TG patient population  
17 without increasing LDL-C.

18           Further, Satoh was a small study conducted in only Japanese patients. This study would  
19 not have been extrapolated to Western populations because the Japanese diet contains much  
20 more fish and has a number of other different attributes. The Japanese consume a higher amount  
21 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference

22 \_\_\_\_\_  
23 <sup>3382</sup> Satoh at 145.

24 <sup>3383</sup> Defendants' Joint Invalidation Contentions at 349-50.



1 states that the results from studies where the patient population is exclusively Japanese cannot be  
2 generalized to other populations.<sup>3384</sup> The Japanese diet comprises between 8 and 15 times more  
3 EPA and DHA than typical the typical Western diet. The Western diet typically consists of  
4 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a  
5 person of ordinary skill would understand that the Japanese respond differently to lipid lowering  
6 agents than Westerners.

7 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))  
8 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.  
9 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without  
10 increasing LDL-C to be a "clinical benefit" is incorrect.<sup>3385</sup> Shinozaki says nothing about an  
11 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by  
12 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."<sup>3386</sup> In  
13 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis  
14 upon which a person of ordinary skill would have sought to combine the composition disclosed  
15 in Shinozaki.

16 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion  
17 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by  
18 Defendants suggest that EPA increases LDL-C.<sup>3387</sup> Defendants identify no other basis upon  
19  
20

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21 <sup>3384</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
22 other populations.").

23 <sup>3385</sup> Defendants' Joint Invalidation Contentions at 349.

24 <sup>3386</sup> Shinozaki at 107-109.

<sup>3387</sup> See, e.g., Rambjor.

1 | which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,  
2 | Satoh, Shinozaki and/or Contacos.

3 | (ii) Geppert and/or Kelley Do  
4 | Not Disclose Purported  
5 | Knowledge that DHA was  
6 | Responsible for the Increase  
7 | in LDL-C

6 | Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
7 | administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
8 | C levels.”<sup>3388</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
9 | known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
10 | rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”  
11 | in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
12 | patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,  
13 | respectively. As discussed above in Section III, a person of ordinary skill would not expect the  
14 | same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or  
15 | Kelley—as in very-high TG patients because patients with higher TG levels had different lipid  
16 | responses compared to patients with lower TG levels. Patients with very-high TG levels were  
17 | considered fundamentally different from patients with borderline-high or high triglycerides from  
18 | a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a  
19 | person of ordinary skill in the art would have expected that fish oils (and other TG lowering  
20 | agents) would not increase LDL-C substantially in patients with normal to borderline high TG

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22 |  
23 | \_\_\_\_\_  
24 | <sup>3388</sup> Defendants’ Joint Invalidity Contentions at 352.

1 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in  
2 patients with very high TG levels.

3 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA  
4 was responsible for the increase in LDL-C levels.”<sup>3389</sup> Both Geppert and Kelley administer  
5 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.  
6 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the  
7 independent effects of DHA because it is not clear how much of the supplement’s effects can be  
8 attributed to DHA.<sup>3390</sup> For example, Defendants’ own prior art teaches that changes in fatty acid  
9 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.<sup>3391</sup>

10 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to  
11 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been  
12 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior  
13 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”<sup>3392</sup> Rather than reading  
14 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior  
15 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there  
16 was confusion in the art and it was unclear whether DHA increased LDL-C.

17 A person of ordinary skill would have expected that Geppert’s results would be  
18 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA  
19 was the only component of fish oil to increase LDL-C. For example, there is no data comparing  
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<sup>3389</sup> Defendants’ Joint Invalidity Contentions at 350.

22 <sup>3390</sup> See Mori 2006 at 96.

23 <sup>3391</sup> Maki at 197.

24 <sup>3392</sup> Geppert at 784.

1 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying  
2 explain the mechanism of LDL-C increase.<sup>3393</sup> A person of ordinary skill would have not  
3 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

4 Defendants contend that Kelley shows that DHA was responsible for the increase in  
5 LDL-C.<sup>3394</sup> In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day  
6 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible  
7 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon  
8 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate  
9 therapy.<sup>3395</sup> Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in  
10 context with the other lipid effects reported in the study. Kelley states that:

11 DHA supplementation may lower the risk of CVD by reducing  
12 plasma triacylglycerols; triacylglycerol:HDL; the number of  
13 small, dense LDL particles; and mean diameter of VLDL particles.  
14 An increase was observed in fasting LDL cholesterol, but it  
15 is unlikely this increase is detrimental because no increase was  
16 observed in the overall number of LDL particles; actually, there  
17 was an 11% reduction that was statistically not significant. The  
18 reason LDL cholesterol increased despite no change in LDL  
19 particle number was that the LDL particles were made larger and  
20 hence more cholesterol rich by DHA treatment.<sup>3396</sup>

21 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation  
22 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle  
23 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
24 concentrations of atherogenic lipids and lipoproteins and increased concentrations of

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21 <sup>3393</sup> *Id.*

22 <sup>3394</sup> Defendants’ Joint Invalidity Contentions at 350.

23 <sup>3395</sup> Kelley at 329.

24 <sup>3396</sup> Kelley at 329

1 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular  
2 health.”<sup>3397</sup> Rather than concluding that DHA was uniquely responsible for a rise in LDL-C  
3 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely  
4 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with  
5 negative attributes, a person of ordinary skill would understand that the reference taught towards  
6 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400  
7 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the  
8 very high TG patient population to be different in terms of their response to lipid therapy,  
9 including administration of DHA. A person of ordinary skill in the art would have expected that  
10 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with  
11 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a  
12 substantial increase in LDL-C in patients with very high TG levels.

13 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was  
14 known that DHA was responsible for the increase in LDL-C levels.

15 Throughout their contentions, Defendants’ selectively cite to data points in a reference  
16 without considering other disclosures or even the reference as a whole. Each reference,  
17 however, must be evaluated for all that it teaches.<sup>3398</sup> As is the case with Kelley, Defendants use  
18 hindsight to characterize a reference based on LDL-C levels alone without considering the other  
19 lipid effects studied, considered and reported.<sup>3399</sup> The isolated manner in which Defendants  
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<sup>3397</sup> Kelley at 324, 332.

22 <sup>3398</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>3399</sup> Kelley at 324 (providing that the objectives of the study were to determine “the effects of DHA supplementation  
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean  
diameters of these particles in fasting and postprandial plasma.”).

1 select such data points is not the approach that a person of ordinary skill would have taken at the  
2 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.  
3 A person of ordinary skill would take into consideration the entire disclosure of a reference,  
4 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,  
5 without explanation, the other effects of DHA that a person of ordinary skill would consider.  
6 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a  
7 favorable effect in hypertriglyceridemic patients.

8 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was  
9 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,  
10 without explanation, other studies that demonstrate that DHA decreases or has little effect on  
11 LDL-C levels.<sup>3400</sup> Defendants identify no other basis upon which a person of ordinary skill  
12 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,  
13 Geppert and/or Kelley.

14 (iv) A Person of Ordinary Skill Would Not Have  
15 been Motivated to Find an Omega-3 Fatty  
16 Acid "Therapy that Would Reduce TG  
17 Levels in Patients with TG Levels  $\geq$ 500  
mg/dL Without Negatively Impacting LDL-  
C Levels."

18 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG  
19 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there  
20 was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,  
21 or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels  
22 for very-high TG patients at the time of the invention. A person of ordinary skill in the art

23 \_\_\_\_\_  
24 <sup>3400</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and  
2 Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were  
3 available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription  
4 omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly  
5 undesirable side effects—including “flushing” (or reddening of the face and other areas with a  
6 burning sensation) and dyspepsia—that limited their usefulness.<sup>3401</sup> Fibrates were effective at  
7 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG  
8 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an  
9 LDL-C lowering medication such as a statin.<sup>3402</sup> However, the risk of rhabdomyolysis increased  
10 five-fold if fibrates were administered with a statin.<sup>3403</sup> Therefore, physicians were reluctant to  
11 recommend, and patients were hesitant embrace, a combination fibrate/statin course of  
12 treatment.<sup>3404</sup> Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to  
13 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,  
14 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

15 In any event, a person of ordinary skill in the art would have understood that omega 3-  
16 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high  
17 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would  
18  
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20 <sup>3401</sup> See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 <sup>3402</sup> Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”);

22 <sup>3403</sup> See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 <sup>3404</sup> See *Id.*, ¶ 17

1 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs  
2 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3405</sup>	-20%	+45%
Lovaza/Omacor <sup>3406</sup>	-6%	+45%

3  
4  
5  
6  
7 That Epadel has been approved for decades but not approved for use in the very high TG  
8 patient population prior to the invention of the asserted patents is a real-world reflection of the  
9 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
10 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
11 been countless studies conducted which administer Epadel and report the effects observed.  
12 Although a few studies administer Epadel to a patient population which included a few patients  
13 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
14 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

15 Defendants offer no “apparent reason” to administer EPA as claimed to patients with  
16 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on  
17 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients  
18 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”<sup>3407</sup>  
19 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500

20  
21  
22 <sup>3405</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

23 <sup>3406</sup> Chan 2002 I at 2381 (Table 3).

24 <sup>3407</sup> Defendants’ Joint Invalidation Contentions at 351-52.



1 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG  
2 reduction and the increased conversion of VLDL to LDL particles.<sup>3408</sup>

3 It was well known at the time of the invention that omega-3 fatty acids, including both  
4 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant  
5 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3  
6 fatty acids worked in part by inhibiting VLDL production and improving the conversion of  
7 VLDL particles to LDL.<sup>3409</sup> A person of ordinary skill in the art understood that EPA and DHA  
8 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when  
9 discussing the TG-lowering mechanism of omega-3 fatty acids.<sup>3410</sup> The discussion related to the  
10 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and  
11 incorporated herein by reference.

12 In fact, it was well understood that the degree of LDL-C elevation observed with  
13 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG  
14 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels  
15 the most in patients with the highest pretreatment TG levels.<sup>3411</sup> Therefore, a person of ordinary  
16 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct  
17 consequence of lowering triglycerides in patients with TG levels  $\geq 500$  mg/dL. The rise in LDL-

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19 <sup>3408</sup> See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese  
20 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and  
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in  
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

21 <sup>3409</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”)

22 <sup>3410</sup> Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*  
23 *Johns Hopkins Textbook of Dyslipidemia* 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

24 <sup>3411</sup> See Bays 2008 Rx Omega-3 p. 402.

1 C was often offset by concurrent treatment with statins.<sup>3412</sup> The safety and efficacy of using  
2 prescription omega-3 in combination with a statin has been well-established.<sup>3413</sup>

3 Although an increase in LDL-C was generally observed when omega-3 fatty acids were  
4 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a  
5 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.  
6 Therefore, the final LDL-C concentration may still be in the normal range.<sup>3414</sup> Furthermore, it  
7 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>3415</sup>

8 In two pivotal studies in very-high TG patients, both of which used prospective,  
9 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL  
10 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).<sup>3416</sup> Correspondingly, prescription  
11 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.<sup>3417</sup> Therefore,  
12 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can  
13 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net  
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15 <sup>3412</sup> See Harris 2008 at 14, McKenney at 722.

16 <sup>3413</sup> McKenney at 722-23.

17 <sup>3414</sup> See Westphal at 918, Harris 1997 at 389.

18 <sup>3415</sup> See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals  
19 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester  
20 transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he  
21 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-  
22 high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the  
treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute  
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this  
rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty  
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in  
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by  
decreased non-HDL-C levels (TC minus HDL-C”).

23 <sup>3416</sup> McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 <sup>3417</sup> McKenney 2007 at 722 (see Fig. 1).

1 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in  
2 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also  
3 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the  
4 number of small, dense LDL particles to larger LDL particles.<sup>3418</sup> Lovaza/Omacor “adversely  
5 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration  
6 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”<sup>3419</sup>  
7 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3  
8 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not  
9 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention  
10 of [coronary heart disease].”<sup>3420</sup>

11 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at  
12 the time of the claimed inventions would have been motivated to find a therapy that would  
13 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting  
14 LDL-C levels,”<sup>3421</sup> one of ordinary skill in the art at the time of the invention understood that the  
15 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with  
16 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to  
17 increase in very-high TG patients, and in some instances the rise was not concerning because  
18 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final  
19 concentration would still be in the normal range. When LDL-C levels increased beyond what  
20 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

21  
22 <sup>3418</sup> McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 <sup>3419</sup> Stalenhoef at 134.

24 <sup>3420</sup> Harris 1997 at 389.

<sup>3421</sup> Defendants’ Joint Invalidation Contentions at 351-52.

1 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of  
2 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to  
3 identify any other basis upon which a person of ordinary skill would have been motivated to find  
4 a therapy that would reduce TG levels in patients with very-high TG levels without negatively  
5 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood  
6 that EPA therapy would *not* reduce Apo-B<sup>3422</sup> (which is a reflection of total atherogenic  
7 lipoproteins)<sup>3423</sup> in very high TG patients, and accordingly would not have been motivated to  
8 administer the claimed EPA composition to the very high TG patient population.

9 Defendants make the conclusory allegation that “routine optimization” by a person of  
10 ordinary skill would yield the claimed invention.<sup>3424</sup> Defendants, however, have offered no  
11 explanation to support that allegation and they further fail to establish any of the required criteria  
12 of “routine optimization” or the prerequisites to this argument. They also fail to provide any  
13 factual detail to support their allegation and they fail to link the allegation to any particular claim  
14 or claim element. Defendants mere allegation constitute an improper placeholder to later  
15 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,  
16 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the  
17 combinations alleged by Defendants and, for the same reasons, it would not be routine to  
18 combine such references. Where, for example, defendants argue that it would be routine to go  
19 from the high TG patient population to the very high TG patient population,<sup>3425</sup> they provide no  
20 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

21 \_\_\_\_\_  
22 <sup>3422</sup> *see* Section V.O.

23 <sup>3423</sup> *see* Section III.

24 <sup>3424</sup> *See, e.g.*, Defendants’ Joint Invalidation Contentions at 347.

<sup>3425</sup> Defendants’ Joint Invalidation Contentions at 354.

1 would have understood these patient populations to be distinct with different impacts of lipid  
2 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would  
3 not have considered the dosage modification suggested by defendants to be routine; Defendants'  
4 argument to the contrary represents hindsight bias.

5 In addition, a person of ordinary skill would have no motivation to combine these  
6 references because EPA would have been expected to have same result as the mixture of EPA  
7 and DHA used in Lovaza/Omacor.

8 (v) A Person of Ordinary Skill Would Not Have  
9 Had a Reasonable Expectation of Success  
10 with the Combinations Defendants  
11 Hypothesize

12 Defendants provide no evidence that a person of ordinary skill would have had a  
13 reasonable expectation of successfully obtaining the claimed invention—a method of reducing  
14 triglycerides in a subject having very-high triglyceride levels by administering EPA of the  
15 recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by  
16 combining the references cited by defendants. For a particular combination of references, there  
17 must be a reasonable expectation that the combination will produce the claimed invention. In  
18 this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with  
19 very-high TG levels.<sup>3426</sup> A person of ordinary skill would have expected EPA, like  
20 Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG  
21 patient population. As discussed in Section III and above, it was well known that TG-lowering

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22 <sup>3426</sup> As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to  
23 have the same TG lowering mechanism and would have further understood that the increase in LDL-C  
24 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of  
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar  
fashion to Lovaza or DHA alone.

agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but caused significant increases in LDL-C levels for patients with very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to expect anything to the contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3427</sup>	-20%	+45%
Lovaza/Omacor <sup>3428</sup>	-6%	+45%

Accordingly, a person of ordinary skill would *not* have a reasonable expectation of success in achieving a reduction in TG levels without substantially increasing LDL-C in patients with very-high TG levels.<sup>3429</sup>

Defendants’ position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to patients with very high triglyceride levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that Defendants’ provide no evidence that anyone thought to administer Epadel.<sup>3430</sup> Epadel was available for many years prior to the invention of the ’652 patent, to patients with very-high TGs as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,

<sup>3427</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

<sup>3428</sup> Chan 2002 I at 2381 (Table 3).

<sup>3429</sup> Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall effect on lipid parameters, teaching away from this combination.

<sup>3430</sup> Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of  
2 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by  
3 Defendants are directed to the use of purified EPA in the very-high TG population.

4 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
5 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
6 countless studies conducted which administer Epadel and report the effects observed. Although  
7 a few studies administer Epadel to a patient population which included a few patients with TG  
8 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
9 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
10 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
11 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
12 triglycerides.

13 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients  
14 with borderline-high/high TG, it would have been obvious to try administering purified ethyl  
15 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants  
16 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of  
17 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.<sup>3431</sup>  
18 Defendants' contentions are no more than a demonstration that certain claim elements was  
19 known in the prior art and demonstrates impermissible hindsight reconstruction.<sup>3432</sup> As is  
20 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,  
21

22 <sup>3431</sup> Defendants' Joint Invalidation Contentions at 354.

23 <sup>3432</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
24 KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.").

EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably, none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

**TABLE 4**  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>3</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>3</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL-apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>4</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>2</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>3-5</sup> One-sample *t* test of difference between baseline and 7 wk: <sup>3</sup>  $P < 0.001$ , <sup>4</sup>  $P < 0.01$ , <sup>5</sup>  $P < 0.05$ .

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.



1 To the extent that Defendants’ arguments are based on results that are not statistically  
2 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not  
3 draw conclusions from these statistically insignificant differences. Indeed, the standard  
4 deviation for the changes reported is greater than the value of the change itself.

5 Defendants argue that it would have been obvious to try administering purified ethyl EPA  
6 to patients with very-high TG levels with a reasonable expectation of success. However, the  
7 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-  
8 try” proves that the claimed invention was obvious where the prior art did not suggest what to  
9 try.<sup>3433</sup> Rather than there being a limited number of options, the state of the art provided a  
10 plethora of compositions and administration protocols associated with multiple kinds of TG-  
11 lowering therapies.<sup>3434</sup> There were not a finite number of options for a person of ordinary skill  
12 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient  
13 population.

14 Defendants argue that a person of ordinary skill at the time of the invention, based on  
15 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone  
16 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to  
17 no impact on LDL-C levels.<sup>3435</sup> However, that statement does not conform with what was  
18 known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high  
19 TG patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor  
20  
21

22 \_\_\_\_\_  
<sup>3433</sup> See *Sanofi*, 748 F.3d at 1360–61.

23 <sup>3434</sup> See *supra* Section III.

24 <sup>3435</sup> Defendants’ Joint Invalidation Contentions at 353.

1 were both known to have little or no effect on LDL-C in patients with borderline-high/high TG  
2 levels.

3 With the lack of any reasonable expectation of success, Defendants argue that their  
4 proposed combination amounts to a simple substitution of one known element for another, and  
5 that that these changes yield predictable results.<sup>3436</sup> Such an argument, however, represents pure  
6 and impermissible hindsight bias and further does not consider that reasons for which a person of  
7 ordinary skill would not be motivated to combine these references and affirmatives ways in  
8 which the art taught away from these combinations.

9 (b) Defendants Have Not Shown It Would Have Been  
10 Obvious to Administer Purified EPA in the Dosing  
Regimen Recited in the Claims

11 (i) The '652 Patent is not Obvious Over WO  
12 '118 or WO '900, in Combination with the  
Lovaza PDR, and Further in View of Leigh-  
13 Firbank and/or Mori 2000

14 With respect to the '652 Patent, Defendants present a combination of five references:  
15 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the  
16 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."<sup>3437</sup> Defendants also  
17 present charts arguing that an additional 61 references may be combined in order to render the  
18 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill  
19 would combine 61 separate references, they additionally do not identify any motivation for  
20  
21

22 \_\_\_\_\_  
23 <sup>3436</sup> Defendants' Joint Invalidation Contentions at 3355.

24 <sup>3437</sup> Defendants' Joint Invalidation Contentions at 356-57.

1 combining these references.<sup>3438, 3439</sup> Although Defendants need not point to an explicit statement  
2 in the prior art motivating the combination of these references, any assertion of an “apparent  
3 reason” to combine must find a basis in the factual record.<sup>3440</sup> Defendants’ unsupported cobbling  
4 of selective disclosures represents hindsight reconstruction.<sup>3441</sup> Defendants’ contentions are no  
5 more than an assertion that certain claim elements were known in the prior art. Throughout their  
6 contentions, Defendants’ selectively cite to data points in a reference without considering other  
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
8  
9

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10 <sup>3438</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of the references cited in  
11 Sections III and V.A. and B., including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi,  
12 Katayama, Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh,  
13 Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert,  
Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a  
person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to  
meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine  
these references. *See* Defendants’ Joint Invalidity Contentions at 356.

14 <sup>3439</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
15 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
16 and that “[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person  
having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 347.

17 <sup>3440</sup> *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point  
“must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation  
to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties  
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.  
Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*  
21 *facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and  
22 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art  
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>3441</sup> *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.<sup>3442</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
2 obviousness.

3 WO '118 is directed at the composition containing EPA for the purpose of preventing the  
4 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118  
5 is directed, "in particular, [to] preventing occurrence of cardiovascular events in  
6 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the  
7 risk of the cardiovascular events."<sup>3443</sup> Contrary to Defendants' assertion that WO '118 discloses  
8 "the administration of 4 g of pure EPA with no DHA,"<sup>3444</sup> WO '118 fails to disclose the claimed  
9 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive  
10 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified  
11 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction  
12 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of  
13 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in  
14 the disclosed composition.<sup>3445</sup>

15 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target  
16 population of the claimed invention. The asserted claims are directed to persons with severe  
17 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only  
18 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.<sup>3446</sup> WO  
19 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

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20  
21 <sup>3442</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 <sup>3443</sup> WO '118 at 9.

23 <sup>3444</sup> Defendants' Joint Invalidation Contentions at 357.

24 <sup>3445</sup> WO '118 at 22-23.

<sup>3446</sup> WO '118 at 8.

1 patients with borderline-high to high TG levels, since the primary goal for patients with very-  
2 high TG is to prevent acute pancreatitis by decreasing TG levels.<sup>3447</sup>

3 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the  
4 effectiveness of the substances for treating hypertriglyceridemia.<sup>3448</sup> WO '118 states that  
5 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-  
6 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +  
7 DHA-E) are not particularly limited as long as intended effects of the present invention are  
8 attained.”<sup>3449</sup> It further states that “the composition is preferably the one having a high purity of  
9 EPA-E and DHA-E.”<sup>3450</sup> Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C,  
10 Apo-B, or Lp-PLA2.

11 WO '900 is directed to a process for producing purified EPA from a culture of micro-  
12 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels  
13 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed  
14 pharmaceutical composition with the specified dosage or administration period, or the claimed  
15 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900  
16 only discloses the method of producing purified EPA for therapeutic use, it does not teach  
17 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient  
18 population or method of treatment.

19  
20  
21 <sup>3447</sup> See Section III.

22 <sup>3448</sup> WO '118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective  
component”).

23 <sup>3449</sup> WO '118 at 22-23.

24 <sup>3450</sup> WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It  
2 lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one  
3 of them.<sup>3451</sup> Moreover, WO '900 does not teach the desired effect of EPA other than  
4 commenting generally that it “may promote health and ameliorate or even reverse the effects of a  
5 range of common diseases.”<sup>3452</sup> It has no discussion, for example, on any TG-lowering effect of  
6 EPA. Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the  
7 *specific* undesired effect of DHA or other impurities it is trying to prevent other than  
8 commenting generally that “the desired effects of EPA may be limited or reversed” by them.<sup>3453</sup>  
9 It has no discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claims of the '652 Patent  
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package  
13 insert specifically) during prosecution.<sup>3454</sup>

14 The analysis of the independent claims of the '652 patent are incorporated into all  
15 asserted claims that depend from those Claims.

16 (a) Leigh-Firbank and Mori 2000 Do  
17 Not Disclose Purported Knowledge  
18  
19

20 <sup>3451</sup> See, e.g., '900 Pub. at 16-17.

21 <sup>3452</sup> '900 Pub. at 5.

22 <sup>3453</sup> '900 Pub. at 39.

23 <sup>3454</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 that DHA was Responsible for the  
2 Increase in LDL-C

3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known  
5 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-  
6 C levels as evidenced by Leigh-Firbank or Mori 2000.”<sup>3455</sup>

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with  
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need  
9 not point to an explicit statement in the prior art motivating the combination of these references,  
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>3456</sup>  
11 Defendants’ unsupported cobbling of selective disclosures represents hindsight  
12 reconstruction.<sup>3457</sup> Defendants’ contentions are no more than an assertion that certain claim  
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to  
14 establish *prima facie* obviousness.

15  
16 <sup>3455</sup> Defendants’ Joint Invalidity Contentions at 357.

17 <sup>3456</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>3457</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that  
2 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank  
3 and Mori 2000 in Section V.G.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank  
4 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and  
5 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does  
6 not offer any disclosure regarding the effect of EPA and DHA separately or gain any  
7 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000  
8 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is  
9 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation  
10 to combine with WO ‘118 or WO ‘900. Engaging in hindsight bias, Defendants ignore, without  
11 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants  
12 fail to identify any other basis upon which a person of ordinary skill would have sought to  
13 combine Mori 2000 with the Lovaza PDR.

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants  
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little  
17 effect on LDL-C levels.<sup>3458</sup> Defendants identify no other basis upon which a person of ordinary  
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or  
19 Mori.

- 20 (ii) The ‘652 Patent is not Obvious Over WO  
21 ‘118, WO ‘900, Grimsgaard, Mori 2000  
22 and/or Maki in Combination with the  
23 Omacor PDR/Lovaza PDR, and Further in

24 <sup>3458</sup> See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.



With respect to the '652 Patent, Defendants present a combination of nine references:

“WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku.”<sup>3459</sup> Defendants also present charts arguing that an additional 56 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 56 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>3460</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>3461</sup> Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

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<sup>3459</sup> Defendants’ Joint Invalidity Contentions at 357.

<sup>3460</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3461</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
2 even the reference as a whole. Each reference, however, must be evaluated for all that it  
3 teaches.<sup>3462</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
4 obviousness.

5 The discussion related to WO ‘118 and WO ‘900 in Section V.G.3.c.1.b.i is incorporated  
6 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section  
7 V.G.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and  
8 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”  
9 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the  
10 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to  
11 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other  
12 basis upon which a person of ordinary skill would have sought to combine the composition  
13 disclosed in Grimsgaard or Mori 2000.

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art  
15 to use EPA as described in WO ’118, WO ‘900, Grimsgaard or Mori 2000 in the treatment  
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their  
17 assertions fail to provide a motivation for combining the references.<sup>3463</sup> Although Defendants  
18 need not point to an explicit statement in the prior art motivating the combination of these  
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual  
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22 \_\_\_\_\_  
23 <sup>3462</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>3463</sup> Defendants’ Joint Invalidation Contentions at 357.

1 record.<sup>3464</sup> Defendants’ assertions related to motivation are insufficient,<sup>3465</sup> and accordingly  
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or  
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference  
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the  
6 manner claimed,<sup>3466</sup> or “a reasonable expectation of success”<sup>3467</sup> of achieving the claimed  
7 invention. Therefore, Defendants should be precluded from relying on this these references.

8 As discussed above in Section V.G.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only  
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both  
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11 <sup>3464</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
12 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
13 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
14 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daichi  
15 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
16 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
17 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
18 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
19 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
20 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
21 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
22 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>3465</sup> For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating  
24 hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any  
basis for that statement. While the paragraph associated with that statement makes assertions regarding the  
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO  
’118. See Defendants’ Joint Invalidity Contentions at 358.

<sup>3466</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.  
Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer  
Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

<sup>3467</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

1 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer  
2 purified EPA to the very high TG patient population and do not provide any reasonable  
3 expectation of success in lowering TG levels in the very high TG patient population without  
4 increasing LDL-C. As discussed above in Section V.G.3.c.1.a.ii.a.i, Takaku candidly  
5 acknowledges that “only a few subjects were examined” and cautions against drawing a  
6 conclusion “only from the results of the present study.”<sup>3468</sup> Further, the study did not include any  
7 placebo control, therefore, a person of ordinary skill in the art would understand these reports do  
8 not provide the ability to conclude that the observed lipid effects would have occurred  
9 independent of the drug that is administered. In addition, the study was conducted exclusively in  
10 Japanese patients, and a person of ordinary skill would not have expected the results to be  
11 applicable to the general population.<sup>3469</sup>

12 The proposed combination does not render the independent claims of the '652 Patent  
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and  
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.<sup>3470</sup>

16 The analysis of the independent claims of the '652 patent are incorporated into all  
17 asserted claims that depend from those Claims.

18 (a) Grimsgaard, Mori 2000 and/or Maki  
19 Do Not Disclose Purported  
20 Knowledge that DHA was

21 <sup>3468</sup> Takaku at ICOSAPENT\_DFNDT00006897.

22 <sup>3469</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.”)

23 <sup>3470</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).

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3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known  
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is  
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or  
7 Maki.”<sup>3471</sup>

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose  
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,  
10 Mori 2000 and/or Maki in Section V.G.3.c.1.a.ii.a.iii is incorporated herein by reference. A  
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA  
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,  
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although  
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not  
15 disclose administration of DHA to the requisite patient population and teaches that DHA is  
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,  
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
18 would consider. Most controlled studies in patients with normal to high baseline TG levels  
19 indicated that DHA had little or no effect on LDL-C.<sup>3472</sup> Therefore, a person of ordinary skill  
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline  
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 <sup>3471</sup> Defendants’ Joint Invalidity Contentions at 358.

23 <sup>3472</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG  
2 levels, a significant increase in LDL-C is observed.<sup>3473</sup> However, one of ordinary skill in the art  
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.<sup>3474</sup>  
4 Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion  
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
8 has little effect on LDL-C levels.<sup>3475</sup> Defendants identify no other basis upon which a person of  
9 ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki,  
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

11 (iii) A Person of Ordinary Skill Would Not Have  
12 Been Motivated to Administer Purified EPA  
13 in the Treatment Regimen Recited in the  
14 Claims

15 For an invention to be obvious, there must have been an "apparent reason" to make it.  
16 Defendants assert that a "person of ordinary skill in the art would have been motivated to  
17 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to  
18 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."<sup>3476</sup> However, as  
19 set forth below, Defendants fail to address why a person of ordinary skill in the art would have  
20 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

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21 <sup>3473</sup> Maki at 195.

22 <sup>3474</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 ("A number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated fat and cholesterol, both of which are known to elevate LDL-C.").

23 <sup>3475</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>3476</sup> Defendants' Joint Invalidity Contentions at 358.

1 greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering  
2 triglycerides *without increasing LDL-C levels*.

3 Indeed, a person of ordinary skill in the art would have understood that omega 3-fatty  
4 acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG  
5 patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not  
6 have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without  
7 increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3477</sup>	-20%	+45%
Lovaza/Omacor <sup>3478</sup>	-6%	+45%

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12 That Epadel has been approved for decades but not approved for use in the very high TG  
13 patient population prior to the invention of the asserted patents is a real-world reflection of the  
14 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
15 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
16 been countless studies conducted which administer Epadel and report the effects observed.  
17 Although a few studies administer Epadel to a patient population which included a few patients  
18 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
19 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

20 Defendants further argue that the disclosure in WO '118 would combine with the prior art  
21 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to

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23 <sup>3477</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>3478</sup> Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118  
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-  
3 purified ethyl-EPA.”<sup>3479</sup> Both of the “reasons” identified by Defendants are false.

4       Regarding Defendants’ first reason, that “products containing DHA were reported to  
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in  
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on  
7 LDL-C.<sup>3480</sup> Therefore, a person of ordinary skill would not have concluded that DHA increases  
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,  
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,  
10 while EPA does not.”<sup>3481</sup> First, Leigh-Firbank cannot comment on the effect of EPA and DHA  
11 alone because it did not administer EPA and DHA separately.<sup>3482</sup> A person of ordinary skill  
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect  
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA  
14 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with  
15 other saturated and polyunsaturated fatty acids.<sup>3483</sup> Therefore, a person of ordinary skill would  
16 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear  
17 how much of the supplement’s effects can be attributed to DHA.<sup>3484</sup> Kelley does not show that

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<sup>3479</sup> Defendants’ Joint Invalidity Contentions at 358-59.

20 <sup>3480</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
21 controlled, found an increase in LDL-C after DHA administration.

22 <sup>3481</sup> Defendants’ Joint Invalidity Contentions at 363.

23 <sup>3482</sup> The discussion related to Leigh-Firbank in Section V.G.3.c.1.a.i.a.iii is incorporated herein by reference.

24 <sup>3483</sup> The discussion related to Kelley in Section V.G.3.c.1.a.iii.a.ii is incorporated herein by reference.

<sup>3484</sup> See Mori 2006 at 96.



1 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a  
2 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase  
3 was induced by fibrate therapy.<sup>3485</sup> Kelley specifically teaches that the increase in LDL-C  
4 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel  
5 increase in overall LDL particle number. Rather than concluding that DHA was uniquely  
6 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to  
7 disclose that DHA had uniquely beneficial cardioprotective effects.<sup>3486</sup> Finally, Theobald also  
8 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for  
9 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by  
10 7% when compared to placebo. However, the DHA composition that was administered in  
11 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,  
12 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA  
13 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it  
14 impossible to determine whether or how much of the supplement’s effects can be attributed to  
15 DHA.<sup>3487</sup> Contrary to Defendants’ assertion that there was “a reported advantage to using EPA  
16 vs. DHA in hypertriglyceridemic subjects,”<sup>3488</sup> there was no known advantage to using EPA vs.  
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately  
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after  
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20 <sup>3485</sup> Kelley at 329.

21 <sup>3486</sup> Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”  
and that “DHA supplementation may improve cardiovascular health.”)

23 <sup>3487</sup> See Mori 2006 at 96.

24 <sup>3488</sup> Defendants’ Joint Invalidation Contentions at 358.

1 EPA supplementation.”<sup>3489</sup> In addition, a person of ordinary skill would have recognized any  
2 impact of DHA reported by the study to be applicable to EPA because they would have  
3 understood these substances to function by the same mechanism. Furthermore, as discussed  
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in  
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients  
6 because patients with higher TG levels had different lipid responses compared to patients with  
7 lower TG levels.

8         Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in  
9 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”  
10 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been  
11 well documented.<sup>3490</sup> Lovaza/Omacor has been shown to reduce the risk for cardiovascular  
12 death plus nonfatal myocardial infarction and nonfatal stroke.<sup>3491</sup> Omega-3 fatty acids have been  
13 shown to exert cardioprotective effects in both primary and secondary coronary heart disease  
14 prevention trials.<sup>3492</sup> Omega-3 fatty acids were known to reduce TG concentration, have  
15 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure  
16 and/or reduce heart rate.<sup>3493</sup>

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19 <sup>3489</sup> Mori 2000 at 1092.

20 <sup>3490</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA  
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 <sup>3491</sup> See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,  
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

22 <sup>3492</sup> Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,  
197 ATEROSCLEROSIS 12, 13 (2008) (“Harris 2008”).

23 <sup>3493</sup> Harris 2008 at 13.  
24

1 Defendants argue that a “person of ordinary skill in the art would have appreciated the  
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce  
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of  
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”<sup>3494</sup> As  
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA  
6 and Lovaza/Omacor have been well documented.<sup>3495</sup>

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart  
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that  
9 DHA is *more* cardioprotective than EPA.<sup>3496</sup> This study found that “depressed levels of long-  
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary  
11 heart disease events.”<sup>3497</sup> Further, the study found that DHA levels, with or without EPA, were  
12 significantly lower in fatal endpoints.<sup>3498</sup> This study suggests that DHA is preferable to EPA—  
13 thus teaching away from the claimed invention.<sup>3499</sup> Defendants rely on hindsight bias to argue  
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA  
15

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16 <sup>3494</sup> Defendants’ Joint Invalidity Contentions at 339.

17 <sup>3495</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA  
18 and CHD risk.”) (“Harris 2007”).

19 <sup>3496</sup> Harris 2007 at 8.

20 <sup>3497</sup> *Id.*

21 <sup>3498</sup> Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all  
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 <sup>3499</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of  
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the  
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*  
*Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs.,*  
*Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the  
prior art ... is strong evidence of nonobviousness.”).

1 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA  
2 was *more* cardioprotective than EPA.

3 Defendants argue that the following claim elements were known: the administration of  
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the  
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to  
6 patients with high and very high TG levels who were not receiving concurrent lipid altering  
7 therapy, and the dose of 4g/day and 12-week regimen.<sup>3500</sup> Defendants then argue that the “only  
8 question is whether one skilled in the art would have been motivated to use the DHA-free,  
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at  
10 least 500 mg/dL as part of the claimed dosage regimen.”<sup>3501</sup>

11 Defendants’ contentions are no more than a recitation that certain claim elements were  
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight  
13 reconstruction.<sup>3502</sup> Notably, Defendants *do not* assert that a person of ordinary skill would have  
14 known that purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL),  
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,<sup>3503</sup>  
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a  
17 number of prior art references disclosed the administration of purified EPA to patients with TG  
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<sup>3500</sup> Defendants’ Joint Invalidity Contentions at 360-61.

21 <sup>3501</sup> Defendants’ Joint Invalidity Contentions at 361.

22 <sup>3502</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 <sup>3503</sup> Nakamura, Matsuzawa, and Takaku.

1 levels > 500 mg/dL.”<sup>3504, 3505</sup> The disclosures of Nakamura (one patient), Matsuzawa (disclosure  
2 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the  
3 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of  
4 ordinary skill in the art would *not* understand these references to relate to the use of EPA in  
5 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions  
6 regarding these references in terms of the very high TG patient population. In Nakamura, one  
7 patient had a baseline TG level > 500 mg/dL.<sup>3506</sup> However, the mean baseline TG for all patients  
8 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was  
9 well below 500 mg/dL.<sup>3507</sup> In Matsuzawa, three patients had TG levels between 400 and 1000  
10 mg/dL and one patient had TG levels > 1,000 mg/dL.<sup>3508</sup> Based on this disclosure, only one  
11 patient definitively had a baseline TG level  $\geq$  500 mg/dL. Further, this one patient was excluded  
12 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol  
13 made it impossible to assess triglyceride levels.”<sup>3509</sup> In Takaku, three patients had baseline TG  
14 levels above 500 mg/dL.<sup>3510</sup> However, the mean baseline TG level for all patients was 245  
15 mg/dL.<sup>3511</sup> Indeed, the mean baseline TG level of the patients in all three studies was well below  
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17 <sup>3504</sup> Defendants’ Joint Invalidity Contentions at 360.

18 <sup>3505</sup> Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500  
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually  
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically  
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 <sup>3506</sup> Nakamura at 23, Table 1.

23 <sup>3507</sup> Nakamura at 23, Tables 1 and 2.

24 <sup>3508</sup> *Id.* at 23.

<sup>3509</sup> *Id.* at 10.

<sup>3510</sup> Takaku at ICOSAPENT\_DFNDTS00006895.

<sup>3511</sup> Takaku at ICOSAPENT\_DFNDTS00006875.

1 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be  
2 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,  
3 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the  
4 Friedewald's Equation cannot be used for patients with triglyceride levels  $\geq$  400 mg/dL.<sup>3512</sup>  
5 Defendants have failed to identify all of the claimed elements and fail to provide motivation to  
6 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with  
7 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated  
9 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the  
10 known TG-lowering effects of highly-purified EPA-E."<sup>3513</sup> This argument is flawed. The prior  
11 art demonstrates a wide range of administration periods utilized in different clinical studies. For  
12 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in  
13 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.  
14 Given the large number of choices of administration periods disclosed in prior art, Defendants  
15 have not shown that a person of ordinary skill would not have been motivated to administer  
16 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

17 Moreover, a person of ordinary skill would not have been motivated to administer highly-  
18 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as  
19 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood  
20 triglycerides.<sup>3514</sup> In fact, Defendants acknowledge in their Joint Invalidity Contentions that

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22 <sup>3512</sup> See Matsuzawa at ICOSAPENT\_DFNDTS00006450.

23 <sup>3513</sup> Defendants' Joint Invalidity Contentions at 361.

24 <sup>3514</sup> Mori 2006 at 98.

1 “DHA and EPA were both known to comparably reduce triglycerides, independently of one  
2 another.”<sup>3515</sup> Data from some studies even suggested that DHA or fish oil may reduce  
3 triglyceride more effectively than EPA.<sup>3516</sup> Therefore, a person of ordinary skill would not have  
4 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination  
5 of EPA and DHA (such as Lovaza) for 12 weeks.

6 Defendants argue that a “person of ordinary skill in the art also would have been  
7 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant  
8 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.<sup>3517</sup> This  
9 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with  
10 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to  
11 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

12 Defendants also, once again, fail to demonstrate that a person of ordinary skill would have  
13 chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such  
14 as Lovaza).

15 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses  
16 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of  
17 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a  
18 dose of 4 g/day rather than a lower dose.”<sup>3518</sup> A person of ordinary skill would not have relied  
19 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,

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21 <sup>3515</sup> Defendants’ Joint Invalidation Contentions at 365.

22 <sup>3516</sup> Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor  
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was  
greater with DHA supplementation than EPA supplementation).

23 <sup>3517</sup> Defendants’ Joint Invalidation Contentions at 361.

24 <sup>3518</sup> Defendants’ Joint Invalidation Contentions at 361.

1 because these studies were not designed to determine the effect of dose on the degree of TG  
2 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower  
3 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

4 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood  
5 triglycerides.<sup>3519</sup> Therefore, a person of ordinary skill would not have been motivated to  
6 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of  
7 EPA and DHA (such as Lovaza).

8 Defendants further argue that a “person of ordinary skill in the art would have also been  
9 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with  
10 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much  
11 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito  
12 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”<sup>3520</sup> This  
13 argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a  
14 greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill  
15 would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any  
16 other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects  
17 having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have  
18 expected that a greater decrease in TG levels, in the very high TG patient population, would lead  
19 to a greater increase in LDL-C levels.

20 Defendants contend that a “person of ordinary skill in the art would have been motivated  
21 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a

22 \_\_\_\_\_  
23 <sup>3519</sup> See Section III.

24 <sup>3520</sup> Defendants’ Joint Invalidity Contentions at 361-62.



1 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to  
2 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”<sup>3521</sup> Defendants first  
3 support this argument by asserting that a person of ordinary skill in the art would have known  
4 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is  
5 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA  
6 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,  
7 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in  
8 V.B.4. and 5” to support this proposition,<sup>3522</sup> however these references do not disclose or suggest  
9 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very  
10 high TG patients.<sup>3523</sup>

11 Defendants next argue again that DHA was known to be responsible for the increase in  
12 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of  
13 ordinary skill would understand that both EPA and DHA function similarly, and that both would  
14 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would  
15 increase LDL-C levels in patients with very high TGs.

16 Defendants argue that a person of ordinary skill in the art “would have known that an  
17 increase in LDL-C was an adverse health effect to be avoided.”<sup>3524</sup> While an increase in LDL-C  
18 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that  
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<sup>3521</sup> Defendants’ Joint Invalidation Contentions at 363.

22 <sup>3522</sup> Defendants’ Joint Invalidation Contentions at 363.

23 <sup>3523</sup> *See* Section IV.

24 <sup>3524</sup> Defendants’ Joint Invalidation Contentions at 365.

1 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3  
2 fatty acids generally, was related to increased conversion of VLDL to LDL particles.<sup>3525</sup>

3 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the  
4 art would have been motivated, with a reasonable expectation of success, to administer a highly-  
5 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in  
6 LDL-C with DHA.”<sup>3526</sup> However, a person of ordinary skill in the art expected an increase in  
7 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time  
8 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant  
9 decrease in the production of VLDL particles and a significant increase in the conversion of  
10 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by  
11 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.<sup>3527</sup> A  
12 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering  
13 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering  
14 mechanism of omega-3 fatty acids.<sup>3528</sup> The discussion related to the TG-lowering mechanism of  
15 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

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20 <sup>3525</sup> See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription  
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly  
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride  
23 levels when given prescription omega-3 therapy”); Chan 2003.

24 <sup>3526</sup> Defendants’ Joint Invalidity Contentions at 365.

<sup>3527</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”).

<sup>3528</sup> Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

1 Further, a person of ordinary skill in the art would have understood that EPA therapy  
2 would *not* reduce Apo-B<sup>3529</sup> (which is a reflection of total atherogenic lipoproteins)<sup>3530</sup> in very  
3 high TG patients, and accordingly would not have been motivated to administer the claimed EPA  
4 composition to the very high TG patient population.

5 Accordingly, a person of ordinary skill would not have been motivated to combine WO  
6 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and  
7 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not  
8 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-  
9 Firbank and/or Mori 2000.

10 (iv) A Person of Ordinary Skill Would Not Have  
11 Had a Reasonable Expectation of Success  
12 with the Combinations Defendants  
Hypothesize

13 Defendants contend that a “person of ordinary skill in the art would have been motivated  
14 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal  
15 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>3531</sup>

16 Defendants also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . .  
17 would have given a person of ordinary skill in the art a reasonable expectation of successfully  
18 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in  
19 these subjects relative to baseline or placebo.”<sup>3532</sup> However, Defendants provide no evidence  
20 that a person or ordinary skill would have had a reasonable expectation of success in a method of

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22 <sup>3529</sup> *see* Section V.O.

23 <sup>3530</sup> *see* Section III.

24 <sup>3531</sup> Defendants’ Joint Invalidity Contentions at 358.

<sup>3532</sup> Defendants’ Joint Invalidity Contentions at 362.

1 reducing triglycerides in a subject having very-high triglyceride levels by administering purified  
2 EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore,  
3 Defendants fail to provide a reasonable expectation of success for the claimed invention.

4 Defendants further argue, that “because it was known that DHA and EPA were  
5 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have  
6 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified  
7 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been  
8 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition  
9 with a reasonable expectation of success that such administration would result in reducing  
10 triglycerides while avoiding an increase in LDL.”<sup>3533</sup> Defendants argument is without any basis.  
11 To the contrary, because a person of ordinary skill in the art would have understood DHA and  
12 EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have  
13 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no  
14 explanation and cite to no article to support their argument that the similar effects on TG levels is  
15 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on  
16 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected  
17 *both* EPA and DHA, whether administered alone or in combination, would cause an increase in  
18 LDL-C when administered to the very high TG patient population.

19 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients  
20 with very-high TG. A person of ordinary skill would have thus expected EPA, like  
21 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient  
22 population. It was well known that TG-lowering agents, specifically fibrates and

23 \_\_\_\_\_  
24 <sup>3533</sup> Defendants’ Joint Invalidity Contentions at 366.

1 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but  
 2 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art  
 3 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the  
 4 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including  
 5 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as  
 6 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3534</sup>	-20%	+45%
Lovaza/Omacor <sup>3535</sup>	-6%	+45%

7 Accordingly, a person of ordinary skill would not have a reasonable expectation of  
 8  
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 11 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients  
 12 with very-high TG levels using EPA.

13 Defendants' position that a person of ordinary skill would have had a reasonable  
 14 expectation of success in administering purified EPA to the requisite patient population to  
 15 achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that  
 16 Defendants' provide no evidence that anyone thought to administer Epadel, which was available  
 17 for many years prior to the invention of the '652 patent, to patients with very-high TGs as a  
 18 treatment. Indeed, none of clinical studies cited by Defendants are directed to the use of purified  
 19 EPA in the very-high TG population.

20 Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990,  
 21 Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been  
 22

23 <sup>3534</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>3535</sup> Chan 2002 I at 2381 (Table 3).

1 countless studies conducted which administer Epadel and report the effects observed. Although  
2 a few studies administer Epadel to a patient population which included a few patients with TG  
3 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration  
4 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not  
5 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as  
6 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high  
7 triglycerides.

8 Accordingly, a person of ordinary skill would not have a reasonable expectation of  
9 success in achieving the claimed invention.

10 (2) Dependent Claims

11 (a) Defendants Have Not Shown that Claims 2 and 11  
12 of the '652 Patent Would Have Been Obvious

13 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
14 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
15 by clear and convincing evidence, they also have not adequately proven the obviousness of  
16 Claims 2 and 11.

17 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach  
18 the additional claim elements of dependent Claims 2 and 11. Defendants contend, without  
19 providing any support, that the claim elements are the results of simply optimizing the conditions  
20 described in the prior art and within the purview of the skilled physicians. These contentions: 1)  
21 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant  
22 to an obvious analysis; 3) fail to address whether the specific combination of claim elements  
23 were all present in the prior art references that would have been combined by a person of  
24 ordinary skill in the art to produce the claimed invention with a reasonable expectation of

1 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
2 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
3 Although convenient and expedient, Defendants’ approach does not conform with the Local  
4 Patent Rules of this District, the law of claim construction, or the law of obviousness.

5 Defendants fail to show a specific combination of references that discloses each element  
6 of the claimed invention. None of the cited references discloses administration of the claimed  
7 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
8 combined to teach the administration of the claimed EPA to very high TG patients.<sup>3536</sup>  
9 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
10 considering other disclosures or even the reference as a whole. Each reference, however, must  
11 be evaluated for all that it teaches.<sup>3537</sup> Defendants’ unsupported cobbling of selective disclosures  
12 represents hindsight reconstruction.<sup>3538</sup>

13 Defendants fail to show a motivation or reason to combine or modify the references  
14 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
15 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not  
16 show why a person of ordinary skill would have been motivated to combine the references to  
17 achieve the claimed invention.<sup>3539</sup>

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19 <sup>3536</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>3537</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>3538</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

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23 <sup>3539</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill

1 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
2 have successfully achieved the claimed invention. In fact, other than simply identifying prior art  
3 references that purportedly disclose disparate elements, Defendants do not even discuss whether  
4 a person of ordinary skill would have expected that the combination to work for its intended  
5 purpose.<sup>3540</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
6 claimed invention.

7 (b) Defendants Have Not Shown that Claims 3 and 12  
8 of the '652 Patent Would Have Been Obvious

9 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
10 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
11 by clear and convincing evidence, they also have not adequately proven the obviousness of  
12 Claims 3 and 12.

13 Defendants contend, without providing meaningful support, that the claim element was  
14 well known in the art. These contentions: 1) do not assert what the prior art discloses to a  
15 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address  
16 whether the specific combination of claim elements were all present in the prior art references  
17 that would have been combined by a person of ordinary skill in the art to produce the claimed  
18 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*  
19 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
20 point of reading the element out of the claim. Although convenient and expedient, Defendants'

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in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness  
determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3540</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)



1 approach does not conform with the Local Patent Rules of this District, the law of claim  
2 construction, or the law of obviousness.

3 Defendants fail to show a specific combination of references that discloses each element  
4 of the claimed invention. Defendants make a conclusory statement that the claimed method of  
5 treatment was well known in the art, but such a naked assertion does not show why a person of  
6 ordinary skill would have been motivated to combine the references to achieve the claimed  
7 invention.<sup>3541</sup> Further Defendants cite to the “Lovaza product” without identifying the prior art  
8 reference to which they refer. Such a reference is inadequate.

9 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
10 have successfully achieved the claimed invention. Defendants do not even discuss whether a  
11 person of ordinary skill would have expected that the combination to work for its intended  
12 purpose.<sup>3542</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
13 claimed invention.

14 (c) Defendants Have Not Shown that Claims 4 and 13  
15 of the ‘652 Patent Would Have Been Obvious

16 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
17 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
18 by clear and convincing evidence, they also have not adequately proven the obviousness of  
19 Claims 4 and 13.

20 \_\_\_\_\_  
21 <sup>3541</sup>*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3542</sup>*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants contend that it would be obvious that a person receiving the claimed EPA  
2 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50  
3 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean  
4 LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for  
5 the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) fail to  
6 address whether the specific combination of claim elements were all present in the prior art  
7 references that would have been combined by a person of ordinary skill in the art to produce the  
8 claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie*  
9 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
10 point of reading the element out of the claim. Although convenient and expedient, Defendants'  
11 approach does not conform with the Local Patent Rules of this District, the law of claim  
12 construction, or the law of obviousness.

13 Defendants fail to show a specific combination of references that discloses each element  
14 of the claimed invention. Defendants merely demonstrate that the element was purported known  
15 in the prior art without explaining how it can be combined with other elements.<sup>3543</sup> As such,  
16 Defendants discuss the claim element in isolation, and fail to address the claimed invention as a  
17 whole.<sup>3544</sup> Defendants selectively cite to an unspecified isolated disclosure within a reference  
18 without considering other disclosures or even the reference as a whole. Each reference,  
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21 <sup>3543</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

23 <sup>3544</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is  
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 | however, must be evaluated for all that it teaches.<sup>3545</sup> Defendants’ unsupported cobbling of  
2 | selective disclosures represents hindsight reconstruction.<sup>3546</sup>

3 |         Because Defendants do not identify any combination of references, they necessarily fail  
4 | to offer any evidence that a person of skill in the art would be motivated to combine those  
5 | references in order to achieve the invention of the claim as a whole. Further, Defendants do not  
6 | discuss at all whether a person of ordinary skill would have been motivated to combine the  
7 | elements, other than stating that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or  
8 | 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment.  
9 | Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150  
10 | mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs  
11 | note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40  
12 | mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would  
13 | have been motivated to combine the elements to achieve the claimed invention.<sup>3547</sup>

14 |         Similarly, without the disclosure of a combination of references and a motivation/reason  
15 | to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
16 | person of ordinary skill in the art would have had a reasonable expectation of success in  
17 | achieving the claimed invention. In fact, other than simply identifying prior art references that  
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19 | <sup>3545</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 | <sup>3546</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
21 | *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
22 | without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 | <sup>3547</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
23 | Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
24 | the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
2 ordinary skill would have expected that the combination to work for its intended purpose for  
3 treating the recited patient population.<sup>3548</sup> As such, Defendants fail to demonstrate reasonable  
4 expectation of success of the claimed invention.

5 (d) Defendants Have Not Shown that Claims 5 and 14  
6 of the '652 Patent Would Have Been Obvious

7 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
8 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
9 by clear and convincing evidence, they also have not adequately proven the obviousness of  
10 Claims 5 and 14.

11 Defendants do not identify any combination of references and simply provide a laundry  
12 list of references without explaining how each reference relates to the claimed invention.  
13 Defendants further contend, without any support, that a person of ordinary skill would have been  
14 able to determine the patient population in need of the claimed methods of treatment, would seek  
15 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat  
16 those patients having very high triglycerides regardless of the baseline values of these lipids.<sup>3549</sup>  
17 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
18 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
19 combination of claim elements were all present in the prior art references that would have been  
20 combined by a person of ordinary skill in the art to produce the claimed invention with a  
21 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants

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22 <sup>3548</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
24 combined, but also that the combination would have worked for its intended purpose.”)

<sup>3549</sup> *Id.*

1 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
2 element out of the claim. Although convenient and expedient, Defendants’ approach does not  
3 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
4 obviousness.

5 Defendants fail to show a specific combination of references that discloses each element  
6 of the claimed invention. Defendants merely list references, without reference to a specific page  
7 or section, that purportedly disclose disparate elements without explaining how they can be  
8 combined.<sup>3550</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
9 the claimed invention as a whole.<sup>3551</sup> Moreover, by simply identifying prior art references  
10 without discussing the specific teachings of each reference, Defendants fail to consider each  
11 prior art reference as a whole.<sup>3552</sup> Each reference must be evaluated for all that it teaches.  
12 Defendants’ unsupported cobbling of selective disclosures represents hindsight  
13 reconstruction.<sup>3553</sup>

14 Because Defendants do not identify any combination of references, they necessarily fail  
15 to offer any evidence that a person of skill in the art would be motivated to combine those  
16 references in order to achieve the invention of the claim as a whole. Defendants make a  
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18 <sup>3550</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*  
19 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>3551</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is  
made with respect to the subject matter as a whole, not separate pieces of the claim”).

21 <sup>3552</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior  
22 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention  
in suit.”) (internal citation and quotation marks omitted).

23 <sup>3553</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed  
2 methods of treatment, without providing a reason that would have prompted a person of ordinary  
3 skill to combine the elements.<sup>3554</sup> Such a naked assertion does not show why a person of  
4 ordinary skill would have been motivated to treat the recited patient population using the claimed  
5 methods of treatment.<sup>3555</sup>

6 Similarly, without the disclosure of a combination of references and a motivation/reason  
7 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
8 person of ordinary skill in the art would have had a reasonable expectation of success in  
9 achieving the claimed invention. In fact, other than simply identifying prior art references that  
10 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
11 ordinary skill would have expected that the combination to work for its intended purpose for  
12 treating the recited patient population.<sup>3556</sup> As such, Defendants fail to demonstrate reasonable  
13 expectation of success of the claimed invention.

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18 <sup>3554</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted)

21 <sup>3555</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3556</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 (e) Defendants Have Not Shown that Claims 6, 7, 15  
2 and 16 of the '652 Patent Would Have Been  
3 Obvious

4 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
5 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
6 by clear and convincing evidence, they also have not adequately proven the obviousness of  
7 Claims 6, 7, 15 and 16.

8 Defendants contend, without support, that the recited reduction in TG represents  
9 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to  
10 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of  
11 ordinary skill to seek to reduce TG by the recited amount because there is no significance  
12 attached to the amount. Defendants conclude, without support, that there was a reasonable  
13 expectation of success without identifying any combination of references and without explaining  
14 how each reference relates to the claimed invention.<sup>3557</sup> These contentions: 1) do not assert  
15 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious  
16 analysis; 3) fail to address whether the specific combination of claim elements were all present in  
17 the prior art references that would have been combined by a person of ordinary skill in the art to  
18 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish  
19 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim  
20 element to the point of reading the element out of the claim. Although convenient and expedient,  
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22 \_\_\_\_\_  
23 <sup>3557</sup> Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris\_Etherton 2002, Kurabayashi, Leigh-  
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney  
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,  
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Defendants' approach does not conform with the Local Patent Rules of this District, the law of  
2 claim construction, or the law of obviousness.

3 Defendants further contend, without support, that a person of ordinary skill would  
4 "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation  
5 containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude,  
6 without support, that it would have been obvious to administer a composition containing EPA,  
7 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while  
8 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to  
9 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim  
10 elements were all present in the prior art references that would have been combined by a person  
11 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of  
12 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
13 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
14 Although convenient and expedient, Defendants' approach does not conform with the Local  
15 Patent Rules of this District, the law of claim construction, or the law of obviousness.

16 Defendants do not identify any combination of references and simply provide a laundry  
17 list of references that purportedly disclose disparate elements without explaining how they can  
18 be combined.<sup>3558</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
19 the claimed invention as a whole.<sup>3559</sup> Defendants selectively cite to an unspecified isolated  
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21 <sup>3558</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*  
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) ("[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art").

23 <sup>3559</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is  
24 made with respect to the subject matter as a whole, not separate pieces of the claim").



1 disclosure within a reference without considering other disclosures or even the reference as a  
2 whole. Each reference, however, must be evaluated for all that it teaches.<sup>3560</sup> Defendants’  
3 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>3561</sup>

4 Because Defendants do not identify any combination of references, they necessarily fail  
5 to offer any evidence that a person of skill in the art would be motivated to combine those  
6 references in order to achieve the invention of the claim as a whole. Defendants make a  
7 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to  
8 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a  
9 person of ordinary skill to reduce triglycerides by the recited amount.<sup>3562</sup> Defendants’ burden to  
10 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”  
11 attached to the recited TG reduction amount.<sup>3563</sup> Defendants have not met the burden with the  
12 naked assertion that it would have been obvious to seek the claim element.

13 Similarly, without the disclosure of a combination of references and a motivation/reason  
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a

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15 <sup>3560</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

16 <sup>3561</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
17 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

18 <sup>3562</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,  
20 1356-57 (Fed. Cir. 2007) (“While the KSR Court rejected a rigid application of the teaching, suggestion, or  
motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason  
21 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the  
claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.  
22 398, 418 (2007)).

23 <sup>3563</sup> Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been  
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*  
24 case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

1 person of ordinary skill in the art would have had a reasonable expectation of success in  
2 achieving the claimed invention. Defendants make a conclusory statement that there was a  
3 reasonable expectation of success, without providing a support other than merely identifying  
4 prior art references that purportedly disclose disparate elements.<sup>3564</sup> The mere fact that elements  
5 are capable of being physically combined does not establish reasonable expectation of  
6 success.<sup>3565</sup>

7 (f) Defendants Have Not Shown that Claims 8 and 17  
8 of the '652 Patent Would Have Been Obvious

9 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
10 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
11 by clear and convincing evidence, they also have not adequately proven the obviousness of  
12 Claims 8 and 17.

13 Defendants offer no reference in support of their contention that these claims are obvious.  
14 Defendants contend, without providing any support, that it would be obvious to one of skill in  
15 the art to administer a composition containing EPA, but containing no DHA, with a reasonable  
16 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These  
17 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;  
18 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of  
19 claim elements were all present in the prior art references that would have been combined by a  
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21 <sup>3564</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
22 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted).

23 <sup>3565</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”).

1 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation  
2 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
3 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
4 Although convenient and expedient, Defendants’ approach does not conform with the Local  
5 Patent Rules of this District, the law of claim construction, or the law of obviousness.

6 Defendants fail to show a specific combination of references that discloses each element  
7 of the claimed invention. None of the cited references discloses administration of the claimed  
8 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
9 combined to teach the administration of the claimed EPA to very high TG patients.<sup>3566</sup>  
10 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
11 considering other disclosures or even the reference as a whole. Each reference, however, must  
12 be evaluated for all that it teaches.<sup>3567</sup> Defendants’ unsupported cobbling of selective disclosures  
13 represents hindsight reconstruction.<sup>3568</sup>

14 Defendants fail to show a motivation or reason to combine or modify the references  
15 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
16 would have been obvious but such a naked assertion does not show why a person of ordinary  
17 skill would have been motivated to combine the references to achieve the claimed invention.<sup>3569</sup>

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19 <sup>3566</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>3567</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>3568</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 <sup>3569</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill

1 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
2 have successfully achieved the claimed invention. In fact, Defendants do not even discuss  
3 whether a person of ordinary skill would have expected that the combination to work for its  
4 intended purpose.<sup>3570</sup> As such, Defendants fail to demonstrate reasonable expectation of success  
5 of the claimed invention.

6 Defendants rely on only one reference in their invalidity contentions with respect to this  
7 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,  
8 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of  
9 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument  
10 and no support for their argument that Theobald makes such a disclosure. Defendants appear to  
11 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all  
12 atherogenic lipoproteins.<sup>3571</sup>

13 Defendants then make the unsupported assertion that “one of ordinary skill in the art  
14 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to  
15 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald  
16 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render  
17 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis  
18 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL  
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21 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
22 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3570</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

<sup>3571</sup> June 26, 2012 Bays Declaration; *see also* Section III.

1 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with  
 2 respect to these claims or Apo-B levels.

3 As discussed above, *see* Section IV, Theobald discloses the administration of a  
 4 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While  
 5 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a  
 6 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of  
 7 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to  
 8 consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following  
 9 administration of the triacylglycerol composition of that reference.<sup>3572</sup>

10 **TABLE 3**  
 Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect <sup>1</sup>
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 <sup>2</sup>	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) <sup>3</sup>
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) <sup>4</sup>
HDL cholesterol (mmol/L) <sup>5</sup>	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) <sup>6</sup>	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
<b>Apolipoprotein B (g/L)</b>	<b>0.84 ± 0.027</b>	<b>0.87 ± 0.026</b>	<b>0.83 ± 0.028</b>	<b>0.84 ± 0.028</b>	<b>0.03 (0.002, 0.055)<sup>7</sup></b>
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) <sup>3</sup>
Weight (kg) <sup>8</sup>	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

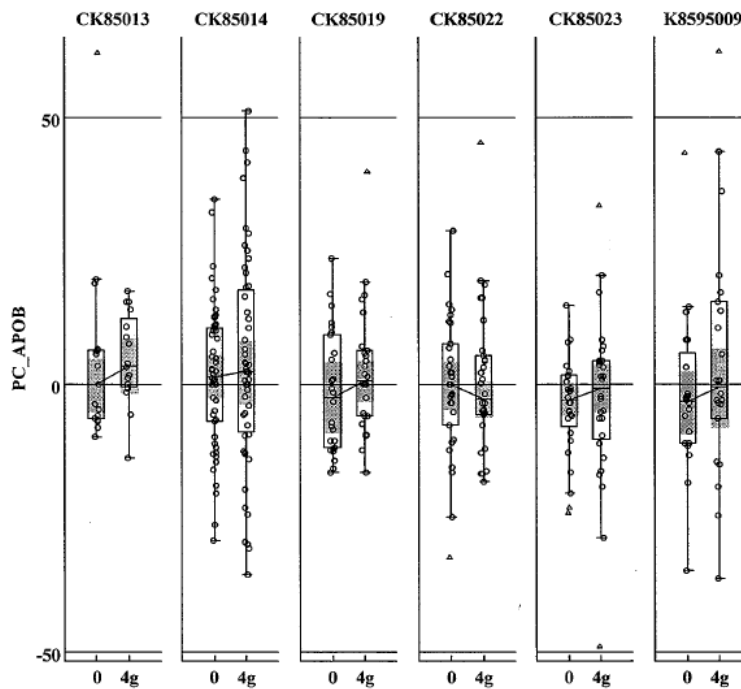
15 <sup>1</sup> Mean difference between active treatment and placebo; 95% CI in parentheses.  
 16 <sup>2</sup>  $\bar{x} \pm \text{SEM}$  (all such values);  $n = 38$ .  
 17 <sup>3,4,7</sup> Paired  $t$  test: <sup>3</sup> $P = 0.04$ , <sup>4</sup> $P = 0.004$ , <sup>7</sup> $P = 0.03$ .  
 18 <sup>5</sup> HDL increased in subjects receiving DHA first. Significant treatment × order effect,  $P = 0.005$ .  
 19 <sup>6</sup>  $n = 37$ ; data were log transformed before analysis by paired  $t$  test.  
 20 <sup>8</sup> Weight increased over the entire study period. Significant order × time effect,  $P = 0.001$ .

21 As discussed above, *see* Section III, a person of skill in the art would not have  
 22 distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a  
 23 person of ordinary skill would have considered Theobald, they would not conclude from the  
 24 reference that EPA therapy decreases Apo-B levels in very high TG patients.

<sup>3572</sup> Theobald at 561, table 3.

1 A person of skill in the art would *not* have understood that EPA therapy in very high TG  
 2 patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked  
 3 to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on  
 4 Apo-B levels in patients with very high TG levels.<sup>3573</sup> The Lovaza clinical trial, which was a  
 5 large study conducted on patients with very high TG levels, shows no difference between a  
 6 placebo-control group and the treatment group with respect to Apo-B levels.<sup>3574</sup>

14. Box plot of individual Category I studies -% change of APOB



19 In each of these studies, including K8595009, where subjects had a median baseline TG  
 20 level of 818 mg/dL,<sup>3575</sup> there was no change in Apo-B between the control and treatment groups.

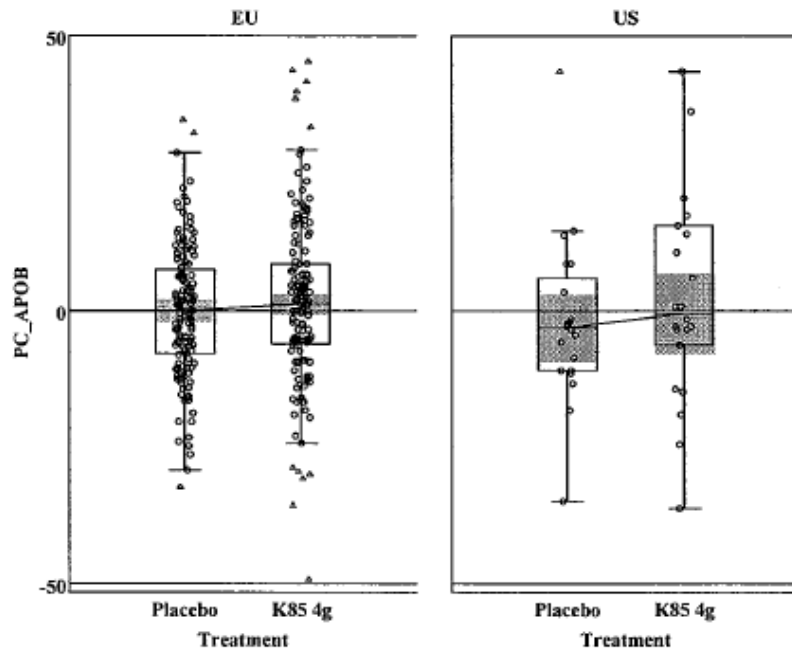
22 <sup>3573</sup> May 8, 2012 Bays Declaration.

23 <sup>3574</sup> Lovaza Approval Package at Table 14.

24 <sup>3575</sup> The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

1 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected  
2 that treatment with Lovaza did not impact Apo-B compared to placebo.<sup>3576</sup>

3  
4 7. Box plot of pooled Category I studies -% change of APOB



16 Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-  
17 B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the  
18 literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.<sup>3577</sup>

19 While Theobald does not even support Defendants' obviousness arguments, their selective  
20 citation of that reference represents impermissible hindsight bias. The examiner had before him  
21 a large number of prior art references reporting Apo-B effects and, even as defendants concede,  
22

23 <sup>3576</sup> Lovaza Approval Package at Table 7.

24 <sup>3577</sup> See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 | agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of  
2 | those references, also reflecting a lack of motivation and no reasonable expectation of  
3 | success.<sup>3578</sup>

4 | Further, a person of skill in the art would have understood Apo-B to be a surrogate for the  
5 | number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.<sup>3579</sup> The person of  
6 | skill in the art would also have recognized that, as TG levels in patients with very high TG levels  
7 | rose, an increasing amount of TGs in those patients were contained within chylomicrons. As  
8 | discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic  
9 | lipoproteins, but instead smaller, denser particles referred to as remnant.<sup>3580</sup> Accordingly,  
10 | because very high TG patients had increasing levels of TGs stored in chylomicrons and because  
11 | chylomicron processing would not have been understood to yield changes in Apo-B, a person of  
12 | skill in the art would have believed that TG-lowering therapies directed to very high TG patients  
13 | would not significantly impact Apo-B.

14 | Accordingly, a person of ordinary skill in the art would not have been motivated to  
15 | replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art  
16 | have been motivated to administer the EPA composition of the claimed invention to very high  
17 | TG patients. For the same reasons, a person of ordinary skill in the art would not have a  
18 | reasonable expectation of success in achieving the claimed invention.

22 | \_\_\_\_\_  
23 | <sup>3578</sup> Defendants' Contentions at 236.

23 | <sup>3579</sup> ATP-III at 3170; Bays 2008 I at 395.

24 | <sup>3580</sup> Kwiterovich in Kwiterovich at 4.



1 (g) Defendants Have Not Shown that Claims 9 and 18  
2 of the '652 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the Independent Claims in  
4 Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims  
5 by clear and convincing evidence, they also have not adequately proven the obviousness of  
6 Claims 9 and 18.

7 Defendants contend that it would have been obvious to use the claimed composition to  
8 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.  
9 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
10 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
11 combination of claim elements were all present in the prior art references that would have been  
12 combined by a person of ordinary skill in the art to produce the claimed invention with a  
13 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
14 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
15 element out of the claim. Although convenient and expedient, Defendants' approach does not  
16 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
17 obviousness.

18 Defendants do not identify any combination of references. Because Defendants do not  
19 identify any combination of references, they necessarily fail to offer any evidence that a person  
20 of skill in the art would be motivated to combine those references in order to achieve the  
21 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of  
22 ordinary skill would have been motivated to combine the elements.<sup>3581</sup> As such, Defendants fail

23 <sup>3581</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
24 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,

1 to demonstrate that there was no motivation to combine the references to achieve the claimed  
2 invention.

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. Defendants make conclusory statements without providing any  
7 support. What is more, Defendants do not even discuss the reasonable expectation of reducing  
8 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of  
9 reducing VLDL-C levels using the claimed methods.

10 **4. The '652 Patent is Not Invalid Under § 112**

11 a) Defendants Have Not Demonstrated that the Claims of the '652  
12 patent Are Invalid for Indefiniteness

13 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]  
14 the subject matter which the applicant regards as his invention.”<sup>3582</sup> Patent claims are valid in  
15 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the  
16 art about the scope of the invention” in light of the specification and the prosecution history.<sup>3583</sup>

17  
18  
19 \_\_\_\_\_  
20 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

21 <sup>3582</sup> Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and  
22 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite  
bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions  
23 other than by making conclusory assertions in return. Therefore, Defendants should be precluded from  
supplementing their naked assertions with new basis in the course of the litigation.

24 <sup>3583</sup> *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

1 The Supreme Court has recognized that “absolute precision is unattainable” in claim language  
2 and “the certainty which the law requires in patents is not greater than is reasonable.”<sup>3584</sup>

3 Defendants allege that a number of terms containing the phrases “about” and  
4 “substantially” are indefinite. Defendants do not provide any reason why these terms are  
5 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,  
6 these terms are routinely used in patent claims, and are not *per se* indefinite.<sup>3585</sup> In particular,  
7 courts have held repeatedly that claims that contain the words “about” and “substantially” are not  
8 indefinite.<sup>3586</sup> Here, a person of ordinary skill would understand with reasonable certainty what  
9 is claimed when the claims are read in light of the specification and prosecution history.<sup>3587</sup>  
10 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being  
11 indefinite.

12 Defendants further allege that the term “4g per day of a pharmaceutical composition  
13 comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” is  
14

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15 <sup>3584</sup> *Id.* at 2129.

16 <sup>3585</sup> *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms  
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the  
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.  
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the  
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d  
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe  
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish  
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 <sup>3586</sup> *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim  
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.  
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction  
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy  
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration  
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,  
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not  
indefinite).

<sup>3587</sup> *See generally* the ’652 patent and its prosecution history.

1 indefinite. They contend that, because there is no indication of how much of the pharmaceutical  
2 composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid  
3 is present in the composition. This is incorrect. A claim can use a ratio to define amounts of  
4 components in a product, using terms such as “percent by weight.”<sup>3588</sup> In light of the  
5 specification and prosecution history, a person of ordinary skill would understand with  
6 reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the  
7 recited pharmaceutical composition in relation to all fatty acids present.<sup>3589</sup> Therefore, these  
8 terms are not indefinite and do not render the claims indefinite.

9 Defendants further allege that the term “compared to baseline” is indefinite. Defendants,  
10 again, provide no basis for this allegation. In light of the specification and the prosecution  
11 history, a person of ordinary skill would know with reasonable certainty the scope of the term  
12 “compared to baseline” and therefore does not render the claims indefinite.

13 Defendants also allege that it is impossible to ascertain the metes and bounds of “a first  
14 patient population having said baseline triglyceride level” and “a second patient population  
15 having said baseline triglycerides level.” A person of ordinary skill, however, would understand  
16 the metes and bounds of the terms in light of the specification and the prosecution history.<sup>3590</sup>  
17 Moreover, the method of comparing a subject to a second subject, such as a placebo controlled,  
18 randomized, double blind study, would have been known to a person of ordinary skill at the time  
19 of the invention. Therefore, the term does not render the claims indefinite.

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21 <sup>3588</sup> *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at \*5–6 (D.N.J.  
22 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a  
23 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at \*10 (E.D. Tex. Apr. 27,  
24 2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total  
volume of the solution, with this ratio expressed as a percentage”).

<sup>3589</sup> See generally the '652 patent and its prosecution history.

<sup>3590</sup> See generally the '652 patent and its prosecution history.

1 Finally, Defendants contend that the asserted claims improperly mix methods and  
2 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that  
3 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness  
4 analysis is based on what the claim language informs a person of ordinary skill in the art in light  
5 of the specification and the prosecution history. Defendants do not identify any actual claim  
6 language that mixes methods and formulations. Moreover, contributory infringement may be  
7 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*  
8 *process . . . knowing the same to be especially made or especially adapted for use in an*  
9 *infringement of such patent.*”<sup>3591</sup> Plaintiffs assert that Defendants’ ANDA products will be used  
10 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound  
11 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are  
12 mistaken and the ’652 patent claims are not indefinite for improperly mixing methods and  
13 formulations.

14 b) Defendants Have Not Demonstrated that the Claims of the ‘652  
15 patent Are Invalid for Insufficient Written Description

16 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a  
17 written description of the invention.” This requires that the specification “reasonably convey” to  
18 a skilled artisan that the applicant “invented” or “had possession” of the claimed subject matter  
19 when the application was filed.<sup>3592</sup> Support need not be literal<sup>3593</sup>—it may be implicit<sup>3594</sup> or

20 <sup>3591</sup> 35 U.S.C. § 271(c) (emphasis added).

21 <sup>3592</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

22 <sup>3593</sup> *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d  
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

23 <sup>3594</sup> *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866  
24 F.2d at 424–25.

1 inherent<sup>3595</sup> in the disclosure. In addition, it is unnecessary to include information that is already  
2 known or available to persons of ordinary skill.<sup>3596</sup>

3 Defendants make three arguments regarding the written description requirement. First,  
4 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack  
5 written description. This is incorrect. The specification of asserted patents literally discloses the  
6 claimed invention.<sup>3597</sup> Moreover, the recited baseline TG levels of the claimed invention appear  
7 in the original claims of the application to which the asserted patent claims priority. Thus, there  
8 is a strong presumption that the claimed invention is adequately described.<sup>3598</sup> Defendants do  
9 not and cannot rebut this presumption. Specifically, the patient population is originally claimed  
10 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500  
11 mg/dl.”<sup>3599</sup> The asserted claims recite the same patient population. Defendants do not contend  
12 that the patient population of the asserted claims is not literally described by the specification  
13 and in the original claims of the application to which the asserted patent claims priority. In fact,  
14 the specification and the provisional patent application claims at the time of filing describe these  
15 limitations.<sup>3600</sup> Therefore, Defendants have failed to explain whether and how an aspect of the  
16

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17 <sup>3595</sup> *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

18 <sup>3596</sup> *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,  
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

19 <sup>3597</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
20 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
legal foundation for claiming that species.”).

21 <sup>3598</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
22 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

23 <sup>3599</sup> See U.S. Application No. 12/702,889.

24 <sup>3600</sup> ‘652 patent at 13:29-34; 14:49-51; U.S. Provisional Application No. 61/151,291.

1 | claimed invention has not been described with sufficient particularity such that one skilled in the  
2 | art would recognize that the applicant had possession of the claimed invention.

3 |         Second, Defendants contend that “a person of skill in the art would not understand that  
4 | the inventor was in possession of a method incorporating [] specific dosages and quantities.”  
5 | Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the  
6 | dosages and quantities of the claimed methods.<sup>3601</sup> Moreover, the dosages and quantities of the  
7 | method appear in the claims, as originally filed. Thus, there is a strong presumption that the  
8 | claimed invention is adequately described.<sup>3602</sup> Defendants do not and cannot rebut this  
9 | presumption. For example, the dosage of the composition was originally claimed as “about 1 g  
10 | to about 4g.”<sup>3603</sup> The asserted claims recite “4 g.” Defendants do not contend that dosages and  
11 | quantities of the asserted claims are not literally described by the specification and in the original  
12 | claims. In fact, the specification and the provisional patent application claims, at the time of  
13 | filing, described these limitations. Therefore, Defendants have failed to explain whether and  
14 | how an aspect of the claimed invention has not been described with sufficient particularity such  
15 | that one skilled in the art would recognize that the applicant had possession of the claimed  
16 | invention.

17 |         Third, Defendants contend that “a person of skill in the art would not understand that the  
18 | inventor was in possession of a method comprising a comparison against a second subject or  
19 |

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20 | <sup>3601</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
21 | inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
22 | legal foundation for claiming that species.”).

23 | <sup>3602</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
24 | initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
a description of the invention defined by the claims”).

<sup>3603</sup> See U.S. Provisional Application No. 61/151,291.

1 against a second population.” The specification demonstrates that the applicants were in  
2 possession of the claimed inventions. For example, a person of ordinary skill would have  
3 understood that the inventor was in possession of a method comprising administration of a  
4 composition with the recited properties, based on a specific comparison of a subject or a  
5 population against a second subject, baseline, or a second population.

6 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,<sup>3604</sup> the court  
7 elaborated that “possession” means possession as evidenced by disclosure. In this case, the  
8 specification of asserted patents literally disclose the claimed invention in the specification and  
9 the claims as originally filed. Thus, an examination of the four corners of the specification from  
10 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the  
11 asserted patents were in possession of the claimed invention.

12 Defendants conclude by alleging that the specification does not describe anything more  
13 than what is obvious, and thus does not provide adequate support for any nonobvious claim.  
14 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the  
15 specification; nonobviousness can be supported by post-filing date evidence for example.<sup>3605</sup>  
16 Written description requires only that the specification reasonably conveys that the applicant had  
17 possession of the claimed subject matter when the application was filed. Therefore, whether the  
18 claims are obvious has no bearing on the adequacy of written description.

19 \_\_\_\_\_  
20 <sup>3604</sup> *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

21 <sup>3605</sup> See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)  
22 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is  
23 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those  
24 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,  
1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained  
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.  
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full  
range of an invention is not always achieved at the time of filing the patent application.”).



1 c) Defendants Have Not Demonstrated that the Claims of the '652  
2 patent Are Invalid for Lack of Enablement

3 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person  
4 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would  
5 require undue experimentation for a person of ordinary skill to make or use the invention.  
6 Factors that may be considered include the quantity of experimentation necessary, the amount of  
7 direction or guidance presented, the presence or absence of working examples, the nature of the  
8 invention, the state of the prior art, the relative skill of those in the art, the predictability or  
9 unpredictability of the art, and the breadth of the claims.<sup>3606</sup> The enablement requirement is  
10 separate and distinct from the written description requirement,<sup>3607</sup> and as such a claim does not  
11 require descriptive support in the disclosure as originally filed for it to be enabled.<sup>3608</sup>

12 Defendants make two specific arguments regarding the enablement requirement. First,  
13 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of  
14 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the  
15 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary  
16 skill would be able to determine the amounts of the components in the pharmaceutical  
17 composition without any experimentation, much less undue experimentation.

18 Second, Defendants contend that it would take undue experimentation to obtain the  
19 claimed required results listed in the full scope of the patent claims, including the claimed lipid  
20 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed  
21 method and certainly not undue experimentation. Administration of a recited amount of a recited

22 \_\_\_\_\_  
<sup>3606</sup> See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 <sup>3607</sup> *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 <sup>3608</sup> MPEP § 2164.

1 composition, for a recited duration, to a specific, recited patient population produces the recited  
2 results. No additional experimentation is required, and Defendants do not explain their  
3 allegation that undue experimentation would be required. Defendants also do not contend that  
4 following the claimed method (each recited element) does not produce the recited results. The  
5 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly  
6 demonstrate that administration of EPA of the recited composition, when administered to  
7 patients with very high TG levels for at least 12 weeks, as specified, produces the recited  
8 results.<sup>3609</sup> Therefore, the claims are not invalid for lack of enablement.

9 Defendants conclude by alleging that the specification does not enable anything more  
10 than what is obvious over the prior art or was known to a person of skill in the art. First,  
11 Defendants do not cite any case or present a legal theory to support this assertion. As such, they  
12 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be  
13 precluded in the future from raising any new legal theory to support this assertion. Moreover,  
14 while the '652 patent's specification enables a person of ordinary skill to obtain the claimed  
15 limitations without undue experiment, the claimed limitations would not have been obvious to a  
16 person of ordinary skill, as discussed in Section V.G.3. Furthermore, Plaintiffs have initiated  
17 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its  
18 claimed methods.<sup>3610, 3611</sup> Therefore, a person of ordinary skill would have concluded that the  
19 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

20  
21 <sup>3609</sup> See VASCEPA Prescribing Information at Table 2.

22 <sup>3610</sup> *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any  
23 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical  
24 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that  
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

<sup>3611</sup> See May 16, 2011 Bays Declaration at Appendix B.

1 H. The '920 Patent

2 1. The '920 Patent Claims Eligible Subject Matter Under § 101

3 Defendants' allegation that the asserted claims of the '920 patent relate to ineligible  
4 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*  
5 case under Section 101 or provide a legal or factual basis to support their allegations.

6 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local  
7 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be  
8 provided.<sup>3612</sup> The bare assertion of invalidity under Section 101 without providing the grounds  
9 for such an allegation and examining the elements of the asserted claims of the '920 patent does  
10 not meet this requirement and thwarts the purpose of the Rules.<sup>3613</sup>

11 The inquiry under Section 101 involves a two-step test: first, a court must determine  
12 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical  
13 phenomenon, or abstract idea.<sup>3614</sup> Second, even if the claim is directed to one of these concepts,  
14 it still may be patent eligible and the court must determine what else is part of the claim.<sup>3615</sup>

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17 <sup>3612</sup> See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all  
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed  
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 <sup>3613</sup> Nor does the preceding paragraph, which provides only a purported summary of the claims of the '920 patent, or  
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the  
21 grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,  
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent  
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide  
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those  
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

22 <sup>3614</sup> *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at  
23 issue are directed to one of those patent-ineligible concepts.”).

24 <sup>3615</sup> *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

1 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*  
2 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of  
3 the '920 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]  
4 conventional” steps, and the only novel element related to administering the proper dosage based  
5 on a natural law observation.<sup>3616</sup> However, the claims merely recited this natural law without  
6 reciting any novel application of it.<sup>3617</sup> The Court found that providing protection to such  
7 claims would result in pre-empting “a broad range of potential uses” and excluding others from  
8 using “the basic tools of scientific and technical work.”<sup>3618</sup> A method of treatment claim,  
9 specifying the subjects, dosage levels, composition, and time course does not raise the concerns  
10 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent  
11 protection.<sup>3619</sup>

12 Defendants suggest that the recited EPA composition of each asserted claim is a naturally  
13 occurring substance. It is not. Even references contained within Defendants’ own contentions  
14 make clear that EPA of the requisite purity and characteristics is not found in nature.<sup>3620</sup> As  
15 expressed by the patents cited in Defendants’ contentions and well-established precedent, for  
16 decades it has been accepted that compositions isolated from nature or purified beyond their

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18 <sup>3616</sup> *Mayo*, 132 S. Ct. at 1294.

19 <sup>3617</sup> *Id.* at 1301.

20 <sup>3618</sup> *Id.*

21 <sup>3619</sup> *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way  
22 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177 , 191-193 (1981) (upholding patentability  
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula  
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d  
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent  
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

<sup>3620</sup> *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative  
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

1 natural state are patent-eligible.<sup>3621</sup> Moreover, Defendants’ assertions are immaterial to a Section  
2 101 defense because method of treatment claims like the ones asserted in this case are patent  
3 eligible even if they are directed to administration of a naturally occurring substance.<sup>3622</sup>

4 To the extent Defendants are arguing that a law of nature both underlies the claims and  
5 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the  
6 claimed effects are the natural result of ingesting a naturally-occurring substance.”<sup>3623</sup> Since the  
7 composition that is the subject of the claims is not naturally occurring, Defendants appear to  
8 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states  
9 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad  
10 characterization of laws of nature.<sup>3624</sup> To say that the claims of the ’920 patent claim a law of  
11 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode  
12 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to  
13 underlying principles of nature” that would “make all inventions unpatentable.”<sup>3625</sup> Indeed, even  
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18 <sup>3621</sup> See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394  
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

19 <sup>3622</sup> *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

20 <sup>3623</sup> See Defendants’ Joint Invalidation Contentions at 388.

21 <sup>3624</sup> See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes  
22 to achieve a desired outcome . . . . That one way of describing the process is to describe the natural ability of the  
subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we  
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability  
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to  
aspirin).”).

23 <sup>3625</sup> See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).  
24

1 those concerned about the implications of *Mayo* on future patents were focused on diagnostic  
2 claims not treatment claims of the type that *Mayo* stated were typical and patentable.<sup>3626</sup>

3 Even if there is some underlying law of nature in the asserted claims, the subject matter  
4 of the '920 patent remains eligible for protection under Section 101. As articulated by *Mayo* and  
5 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to  
6 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to  
7 foreclose from others the use of that equation in conjunction with all of the other steps in their  
8 claimed process.’”<sup>3627</sup> As discussed above, the asserted claims of the '920 patent contain a  
9 novel, unconventional, and specific method of treatment comprising a particularized application  
10 of a nonnaturally occurring substance and does not preempt the use of a law of nature.<sup>3628</sup>

11 Defendants also argue that any argument by Amarin in response to Defendants’ § 112  
12 arguments are further evidence of invalidity under § 101. This argument is without merit. The  
13 claims are enabled and written description is satisfied for the reasons discussed below. In  
14 addition, as discussed above, the asserted claims are not merely a naturally-occurring  
15 phenomena, and thus satisfy the requirements of § 101.

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20 <sup>3626</sup> See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying  
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,  
particularly in the area of diagnostic research.”).

22 <sup>3627</sup> See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 <sup>3628</sup> See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at \*4 (C.D. Cal. July 24, 2012)  
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was  
“just one step in the whole process” claimed by the invention).

1                   **2.       The Asserted Claims of the ‘920 Patent Are Not Anticipated by WO**  
2                   **‘118**

3                   To anticipate, a single prior art reference must sufficiently describe a claimed  
4 invention so that the public is in “possession” of that invention.<sup>3629</sup> Therefore, to anticipate, a  
5 reference must set forth every element of the claim, either expressly or inherently, in as complete  
6 detail as is contained in the claim.<sup>3630</sup> The claim elements must also be “arranged” in the prior  
7 art reference, just as they are in the claim,<sup>3631</sup> rather than as “multiple, distinct teachings that the  
8 artisan might somehow combine to achieve the claimed invention.”<sup>3632</sup> In addition, public  
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the  
10 invention without undue experimentation.<sup>3633</sup> Factors that may be included in this analysis  
11 include the quantity of experimentation necessary, the amount of direction or guidance  
12 presented, the presence or absence of working examples, the nature of the invention, the state of  
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,  
14 and the breadth of the claims.<sup>3634</sup> This inquiry is objective, and thus evidence of undue  
15 experimentation need not be prior art.<sup>3635</sup>

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<sup>3629</sup> *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 <sup>3630</sup> *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.  
18 Cir. 1989).

<sup>3631</sup> *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 <sup>3632</sup> *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587  
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

20 <sup>3633</sup> *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,*  
21 *Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

<sup>3634</sup> *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 <sup>3635</sup> *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999  
23 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.  
24 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822  
F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-10 of the '920 Patent are anticipated by the WO '118  
2 reference.<sup>3636</sup>

3 A element-by-element analysis, identifying each element of each asserted claim that is  
4 absent from WO '118, is provided below. The contentions below are incorporated by reference  
5 into Exhibit H, and vice-versa. WO '118 does not anticipate the claims of the '920 patent  
6 because it does not describe, properly arrange, or enable the '920 patent claims.

7 a) WO '118 Does Not Teach Every Element of the Claims of the  
8 '920 Patent

9 (1) WO '118 Does Not Describe the Claimed Lipid Effects

10 It is well established that, for a prior art reference to anticipate, “every element of the  
11 claimed invention must be identically shown in a single reference.”<sup>3637</sup> Moreover, the elements  
12 of the claimed invention must have “strict identity” with the elements of the reference; “minimal  
13 and obvious” differences are sufficient to prevent anticipation.<sup>3638</sup> Here, WO '118 entirely fails  
14 to disclose the following elements of Claim 1 of the '920 Patent: *to effect a reduction in*  
15 *triglycerides compared to baseline*. Defendants appear to concede that WO '118 does not  
16 expressly teach these elements, as they fail to set forth any basis for concluding that WO '118  
17 teaches this element.<sup>3639</sup> Indeed, Defendants could not set forth any basis for concluding that  
18 WO '118 teaches this element because WO '118 does not.

19 Instead, Defendants argue that these elements express the intended result of a method that

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21 <sup>3636</sup> References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs  
reserve their right to obtain a certified translation of WO '118.

22 <sup>3637</sup> *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*  
*Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

23 <sup>3638</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 <sup>3639</sup> Defendants' Invalidation Contentions at 202-204.



1 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth  
2 below, WO '118 fails to disclose each element of the independent claim of the '920 Patent, either  
3 expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants  
4 also argue that these elements represent inherent, natural properties of EPA, and are entitled to  
5 no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation  
6 and claim construction. Further, while Defendants argue that the inherent properties are  
7 exemplified in the prior art, they fail to identify even a single prior art reference that makes such  
8 a disclosure. Defendants cannot point to a single, specific prior art reference because the  
9 claimed pharmaceutical composition has never been administered in the manner claimed to the  
10 claimed patient population. Also, these elements are positively recited in the body of the claim  
11 and therefore cannot be construed as a non-limiting preamble and must be given patentable  
12 weight.

13 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid  
14 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
15 inherently anticipate as a matter of law.”<sup>3640</sup> “[A]nticipation by inherent disclosure is appropriate  
16 only when the reference discloses prior art that must *necessarily* include the unstated  
17 limitation.”<sup>3641</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
18 possibly present’ in the prior art.”<sup>3642</sup> WO '118 fails to provide any data related to the lipid  
19 effects of the disclosed invention on patients described in the publication. Therefore, Defendants  
20 fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets  
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<sup>3640</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>3641</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 <sup>3642</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 the elements of the independent claim every time it is administered.

2 Defendants fail to demonstrate that administration of the claimed EPA compositions  
3 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants  
4 suggests that EPA administration may increase LDL-C.<sup>3643</sup> Rambjor is a clinical study which  
5 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA  
6 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a  
7 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*  
8 decrease TG without increasing LDL-C *every time it is administered*.

9 Therefore, WO ‘118 cannot anticipate the independent claim of the ‘920 patent. Because  
10 the dependent claims include all of the claim elements of the independent claim, WO’ 118  
11 cannot anticipate any of the dependent claims as well.

12 (2) WO ‘118 Does Not Disclose Methods of Treating The  
13 Claimed Patient Population

14 In addition, WO ‘118 fails to disclose or suggest the claimed pharmaceutical composition  
15 be administered in the manner claimed to the claimed patient population. Defendants attempt to  
16 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is  
17 the introductory clause of a patent claim and includes everything from the beginning of the claim  
18 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the  
19 preamble.

20 A claim preamble has patentable weight if, “when read in the context of the entire claim,  
21 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,  
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24 <sup>3643</sup> See, e.g., Rambjor.

1 and vitality’ to the claim.”<sup>3644</sup> Additionally, the preamble constitutes a claim element when the  
2 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and  
3 claim body to define the claimed limitation.”<sup>3645</sup>

4 The preamble of the asserted claims is limiting for several reasons. The term “subject” in  
5 the preamble of the independent claim defines and provides antecedent basis for the “subject”  
6 recited in the body of the claims. When reading the claim, one must rely on both the preamble  
7 and the claim body to define the claimed invention.

8 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is  
9 properly construed as a limitation of the claim itself.”<sup>3646</sup> The recitation of a “method of  
10 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing  
11 triglycerides in the body of the claim and emphasizes the intentional purpose for which the  
12 method must be performed - to reduce triglycerides.

13 It is clear that “the claim drafter chose to use both the preamble and the body of the claim  
14 to define the subject matter of the claimed invention.”<sup>3647</sup> Thus, the entire preamble in the  
15 independent claim of the ‘920 must contain patentable weight.

16 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.  
17 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be  
18 administered in the manner claimed to the claimed patient population.

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20 <sup>3644</sup> *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 <sup>3645</sup> *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 <sup>3646</sup> *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*  
*Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases  
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a  
necessary and defining aspect of the invention, specifically its portability,” and because the specification and  
prosecution history “emphasize this feature of the invention”).

24 <sup>3647</sup> *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 First, WO '118 fails to expressly disclose “a method of reducing triglycerides.” In fact,  
2 the invention disclosed by WO '118 relates to a composition for **preventing occurrence of**  
3 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the  
4 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence  
5 of cardiovascular events is defined in WO '118 as “all cases of primary prevention, and  
6 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden  
7 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest  
8 angina and exercise-induced angina, and destabilization of the angina.”<sup>3648</sup> The invention of WO  
9 '118 is intended to be administered to any person in need of prevention of the occurrence of  
10 cardiovascular events, who are typically hypercholesterolemia patients.<sup>3649</sup> WO '118 does not  
11 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot  
12 anticipate the independent claim.

13 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail  
14 to prove that these elements of the claimed invention have “strict identity” with the elements of  
15 the reference.<sup>3650</sup> WO '118 fails to anticipate this claim element because the broad disclosure  
16 fails to anticipate the narrow claimed range, and the specific patient population defined in the  
17 claims is an essential part of the claimed invention.

18 There is no evidence in that subject as described in the claims were ever treated. In fact,  
19 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the  
20 definition of “hypertriglyceridemia” in WO '118 to argue that WO '118 discloses treatment of  
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<sup>3648</sup> WO '118 at 12.

23 <sup>3649</sup> *Id.*

24 <sup>3650</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 the subject as described in the claims. It does not. Defendants' argument rests on the definition  
2 in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150  
3 mg/dL." WO '118's definition is not tied to a specific subject and there are no working  
4 examples, data or other reference in WO '118 indicating that any subject with fasting TG levels  
5 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any  
6 EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as  
7 evidence that a "person of ordinary skill in the art would have understood that the term  
8 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of  
9 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable  
10 and then merely provides examples of commercially available "soft capsules," such as Omacor.  
11 The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients  
12 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be  
13 used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably'  
14 or 'possibly' meets the claims cannot inherently anticipate as a matter of law."<sup>3651</sup> Therefore,  
15 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO  
16 '118 meets the claim elements of the independent claim every time it is administered.

17 Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges  
18 claimed by the '920 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500  
19 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between  
20 330 and 450 degrees. The court found that the broader prior art range could not anticipate the  
21 claimed temperature range, "[g]iven the considerable difference between the claimed range and  
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23 <sup>3651</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).  
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1 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the  
2 claimed range with sufficient specificity to anticipate this element of the claim.”<sup>3652</sup> A prior art’s  
3 teaching of a broad genus does not necessarily disclose every species within that genus. The  
4 court explained the slightly overlapping range between the preferred range and claimed range “is  
5 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>3653</sup> and therefore  
6 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of  
7 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not  
8 anticipate the subject as described in the claims because it fails to described the claimed TG  
9 range with sufficient specificity.

10 The court in *Atofina* ruled on an additional question of anticipation that also involved a  
11 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as  
12 compared to the patent’s claimed range of 0.1 to 5.0 percent.<sup>3654</sup> The court explained that  
13 “although there is a slight overlap, no reasonable fact finder could determine that this overlap  
14 describes the entire claimed range with sufficient specificity to anticipate this limitation of the  
15 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”<sup>3655</sup> Similarly,  
16 although there may be overlap between the definition of hypertriglyceridemia taught by WO  
17 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not  
18 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500  
19 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of  
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21 <sup>3652</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

22 <sup>3653</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>3654</sup> *Id.*

24 <sup>3655</sup> *Id.*

1 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels  
2 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic  
3 events as the primary clinical objective),<sup>3656</sup> WO '118, therefore, does not expressly disclose the  
4 specific patient population that is an essential element of the claims of the asserted patents.  
5 Therefore, WO '118 cannot anticipate the claims of the asserted patents.

6 The treatment of a patient with elevated TG levels varies depending on their serum  
7 triglyceride levels. Identification of the patient population with very high TG levels (at least 500  
8 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,  
9 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment  
10 of lipid disorders.<sup>3657</sup> The ATP-III divided hypertriglyceridemia patients into three classes based  
11 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),  
12 and very-high TGs ( $\geq 500$  mg/dL)—and recommended substantially different treatment  
13 strategies for patients depending on classification.<sup>3658</sup> For the borderline-high and high TG  
14 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.<sup>3659</sup>  
15 Accordingly, in these populations, physicians focused on lowering LDL-C.<sup>3660</sup> In this patient  
16 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.  
17 In contrast, the primary goal for very-high TG patients ( $\geq 500$  mg/dL) was to reduce the risk of  
18 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated  
19 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary

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20 <sup>3656</sup> See Section III.

21 <sup>3657</sup> *Id.*

22 <sup>3658</sup> ATP III at 3335; *See also* Section III.

23 <sup>3659</sup> *Id.*

24 <sup>3660</sup> *Id.*

1 treatment goal.<sup>3661</sup> Therefore, as evidenced by the ATP-III, patients with very-high TG levels  
2 were considered fundamentally different from patients with borderline-high or high TGs from a  
3 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

4 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride  
5 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In  
6 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at  
7 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular  
8 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).  
9 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels  
10 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by  
11 decreasing triglycerides), as required by the independent claims of the asserted patents, and  
12 therefore cannot anticipate the independent claim of the ‘920 Patent.

13 (3) WO ‘118 Does Not Describe the Claimed Pharmaceutical  
14 Composition or its Specific Administration

15 WO ‘118 further does not anticipate the claims of the ‘920 patent because it does not  
16 disclose “administering orally to the subject.” As WO ‘118 fails to disclose the subject as  
17 claimed, it cannot anticipate oral administration to the claimed “subject.”

18 WO ‘118 additionally cannot anticipate the claims of the ‘920 patent because it does not  
19 disclose administering the pharmaceutical composition at a dose of about 4g per day.  
20 Defendants argue that this element is disclosed by WO ‘118’s teaching that the daily dose is  
21 “typically 0.3 to 6 g/day.” Defendants fail to provide the entire disclosure of WO ‘118, which  
22 states that the daily dose is “typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more

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<sup>3661</sup> *Id.*



1 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8  
2 g.day. Another preferable fatty acid included is DHA-E.” WO ‘118 teaches that the dosage is  
3 not particularly limited as long as the intended effect, preventing the occurrence of  
4 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose  
5 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be  
6 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no  
7 working examples, data or other reference in WO ‘118 indicating that any subject (much less  
8 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the  
9 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

10 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of  
11 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The  
12 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic  
13 range of 330 to 450 °C,”<sup>3662</sup> and therefore failed to anticipate the claimed range. The court in  
14 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate  
15 the patent’s claimed range of 0.1 to 5.0 percent.<sup>3663</sup> The court explained that “although there is a  
16 slight overlap, no reasonable fact finder could determine that this overlap describes the entire  
17 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are  
18 different, not the same. . . . Thus, there is no anticipation.”<sup>3664</sup> Similarly, although there may be  
19 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘920  
20 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range  
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<sup>3662</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>3663</sup> *Id.*

24 <sup>3664</sup> *Id.*

1 claimed by the '920 patent does not fall within WO '118's preferred range. Defendants  
2 conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably,  
3 the example indicates that up to 900 mg of the EPA composition could be used three times per  
4 day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '920  
5 patent and cannot anticipate the independent claim of the '920 Patent.

6 WO '118 further does not anticipate the claims of the '920 patent because it does not  
7 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a  
8 portion of the disclosure and exclude sections that show the breadth of WO '118's teachings.  
9 WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high  
10 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and  
11 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or  
12 higher, and still more preferably 96.5% by weight or higher."<sup>3665</sup> Therefore, WO '118 discloses  
13 EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total  
14 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed  
15 generic range for the EPA composition in the claimed pharmaceutical composition.

16 The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the  
17 . . . range claimed in the" patent is insufficient for anticipation.<sup>3666</sup> In *Atofina*, the prior art  
18 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a  
19 range between 330 and 450 degrees. The court explained that this slight overlap "is not  
20 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"<sup>3667</sup> and therefore failed

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22 <sup>3665</sup> WO '118 at 22.

23 <sup>3666</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

24 <sup>3667</sup> *Atofina*, 441 F.3d at 1000.

1 to anticipate the claimed range.<sup>3668</sup> The court in *Atofina* also found that a prior art disclosure of a  
2 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0  
3 percent.<sup>3669</sup> The court explained that “although there is a slight overlap, no reasonable fact finder  
4 could determine that this overlap describes the entire claimed range with sufficient specificity to  
5 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no  
6 anticipation.”<sup>3670</sup>

7 Similarly, although there may be some overlap between the E-EPA content disclosed by  
8 WO ‘118 and the ranges claimed by the ‘920 patent, WO ‘118 does not specifically highlight the  
9 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a  
10 critical factor of the invention disclosed in the ‘920 patent. Therefore, WO ‘118’s broad  
11 disclosure of the E-EPA content in its invention does not describe the claimed range with  
12 sufficient specificity and cannot anticipate the independent claim of the ‘920 patent.

13 WO ‘118 is additionally insufficient for anticipation because it does not expressly  
14 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118  
15 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is  
16 DHA-E.”<sup>3671</sup> The disclosure goes on to state that the composition of the invention is preferably  
17 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed  
18 pharmaceutical composition is a critical factor of the invention disclosed in the ‘920 patent.

19 The disclosure of WO ‘118 treats DHA and EPA interchangeably. The disclosed  
20 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.

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22 <sup>3668</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>3669</sup> *Id.*

24 <sup>3670</sup> *Id.*

<sup>3671</sup> WO ‘118 at 22.

1 There is no express teaching or guidance directing the person of ordinary skill in the art to the  
2 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no  
3 difference between the use of EPA or DHA in its invention, cannot anticipate the independent  
4 claim of the '920 patent.

5 Defendants contend that Plaintiffs are estopped from arguing there is any material  
6 difference between "not more than about 4% DHA" and "substantially no DHA." Defendants  
7 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing  
8 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is  
9 without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and  
10 Defendants have cited no authority to support their position suggesting the contrary. The  
11 language of "not more than about 4% DHA" and "substantially no DHA" are different phrases  
12 and are not co-extensive. Accordingly, plaintiffs are not estopped.

13 In the same paragraph containing their allegation of estoppel, Defendants also quote from  
14 Amarin's 2011 10-K. It is unclear whether these quotations are associated with their  
15 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these  
16 statements form the basis for any theory of estoppel. To the extent that Defendants quote  
17 Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The  
18 quoted statements do not identify any recited claim element, including the specific  
19 pharmaceutical composition, the recited patient population, administration in the manner  
20 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from  
21 the quoted statements.

22 (4) WO '118 Does Not Describe the Dependent Claims

23 Defendants fail to address any of the claim elements of the dependent claims.  
24 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail

1 to set forth any meaningful basis for concluding that WO '118 teaches these elements.  
2 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by  
3 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to  
4 no patentable weight.” To the extent the recited claim elements relate to the administration step,  
5 the dosage form or characteristics of the treated subject and the specific effect produced by the  
6 claimed method, Defendants’ contentions that the claim limitations are inherent properties of  
7 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO  
8 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.  
9 Defendants have not met the burden to establish anticipation with the naked assertion that the  
10 effects are inherent, natural properties of EPA.

11 Further, Defendants entirely fail to prove that inherently discloses the recited claim  
12 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
13 inherently anticipate as a matter of law.”<sup>3672</sup> “[A]nticipation by inherent disclosure is appropriate  
14 only when the reference discloses prior art that must *necessarily* include the unstated  
15 limitation.”<sup>3673</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
16 possibly present’ in the prior art.”<sup>3674</sup> Defendants fail to show that WO '118 “*necessarily*” meets  
17 the recited claim elements relating to the administration step, the dosage form or characteristics  
18 of the treated subject and the specific effect produced by the claimed method *every time*. WO  
19 '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total  
20 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in  
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<sup>3672</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>3673</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 <sup>3674</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to,  
2 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and  
3 convincing evidence that the composition disclosed by WO '118 meets any dependent claim  
4 elements.

5 **3. The Claims of the '920 Patent Would Not Have Been Obvious In**  
6 **Light of the Asserted References**

7 Defendants identify 77 separate references that it asserts somehow render the claims of  
8 the '920 patent obvious.<sup>3675</sup> Defendants fail to demonstrate by clear and convincing evidence  
9 that any of these references, alone or in combination, would render obvious any claims of the  
10 '920 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of  
11 the '920 patent itself to guide its combination of references.<sup>3676</sup> Defendants chart a laundry list  
12 of 77 separate references, without explanation. Defendants' disclosures do not comply with  
13 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly  
14 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs  
15 cannot respond to undisclosed combinations and arguments.<sup>3677</sup>

16 Despite the general, non-limiting nature of Defendants' Joint Invalidation Contentions,  
17 Plaintiffs have discerned and will specifically respond to the following alleged prior art  
18 combinations:

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<sup>3675</sup> Defendants' Joint Invalidation Contentions at 13-25.

20 <sup>3676</sup> *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention  
21 as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is  
obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 <sup>3677</sup> This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,  
23 including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for  
EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the  
24 Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that  
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to  
rely on undisclosed or insufficiently disclosed references or argument.

- 1 • 1) “. . .the asserted claims of the ’920 patent would have been obvious over the  
2 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
3 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in  
4 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori  
5 2000.”
- 6 • 2) “. . .the asserted claims of the ’920 patent would have been obvious over the  
7 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
8 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,  
9 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori  
10 2000 and/or Maki.”
- 11 • 3) “. . .the asserted claims of the ’920 patent would have been obvious over the  
12 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
13 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view  
14 of Satoh or Shinozaki in further view of Contacos.”
- 15 • 4) “. . . the asserted claims of the ’920 patent would have been obvious over WO ’118  
16 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the  
17 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 18 • 5) “. . . the asserted claims of the ’920 patent would have been obvious over WO  
19 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment  
20 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and  
21 further in view of Katayama, Matsuzawa and/or Takaku.”

22 A patent claim is invalid “if the differences between the subject matter sought to be  
23 patented and the prior art are such that the subject matter as a whole would have been obvious at  
24 the time the invention was made to a person having ordinary skill in the art.”<sup>3678</sup> Obviousness is  
a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,  
(2) the scope and content of the prior art, and (3) the differences between the prior art and the  
claims at issue.<sup>3679</sup>

In evaluating obviousness, each prior art reference must be evaluated for all that it

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<sup>3678</sup> 35 U.S.C. § 103(a).

<sup>3679</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1 teaches, including the portions that would lead away from the claimed invention.<sup>3680</sup> Indeed, any  
2 teaching in the art that points away from the claimed invention must be considered.<sup>3681</sup> A  
3 reference teaches away if a person of ordinary skill, upon reading the reference, would be  
4 discouraged from following the path set out in the reference, or would be led in a direction  
5 divergent from the path that was taken by the applicant.<sup>3682</sup> For instance, a reference teaches  
6 away if it suggests that the line of development flowing from the reference’s disclosure is  
7 unlikely to be productive of the result sought by the applicant.<sup>3683</sup>

8 In order to find obviousness based on a combination of references, there must be some  
9 rationale for combining the references in the way claimed that is separate and apart from the  
10 hindsight provided by the patented invention itself.<sup>3684</sup> The law prohibits an obviousness  
11 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art  
12 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of  
13 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed  
14 invention.”<sup>3685</sup> “The invention must be viewed not after the blueprint has been drawn by the  
15 inventor, but as it would have been perceived in the state of the art that existed at the time the  
16 invention was made.”<sup>3686</sup>

17 “The determination of obviousness is made with respect to the subject matter as a whole,  
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19 <sup>3680</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 <sup>3681</sup> *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

21 <sup>3682</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

22 <sup>3683</sup> *Id.*

23 <sup>3684</sup> *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

24 <sup>3685</sup> *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

<sup>3686</sup> *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)



1 not separate pieces of the claim.”<sup>3687</sup> “[A] patent composed of several elements is not proved  
2 obvious merely by demonstrating that each of its elements was, independently, known in the  
3 prior art.”<sup>3688</sup> “This is so because inventions in most, if not all, instances rely upon building  
4 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations  
5 of what, in some sense, is already known.”<sup>3689</sup>

6 Accordingly, it is improper to pick and choose isolated elements from the prior art and  
7 combine them so as to yield the invention<sup>3690</sup> or to modify a prior art reference in a way that  
8 “would destroy the fundamental characteristics of that reference.”<sup>3691</sup> Moreover, a combination  
9 is not obvious where “it would be impossible to apply these teachings [of the secondary  
10 reference] to the [primary reference] without entirely changing the basic mechanism and  
11 procedure thereof,”<sup>3692</sup> or where the proposed combination requires “material and radical  
12 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the  
13 prior art device.<sup>3693</sup> Furthermore, it is improper “to modify the secondary reference before it is  
14 employed to modify the primary reference” in assessing obviousness.<sup>3694</sup>

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18 <sup>3687</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

19 <sup>3688</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

20 <sup>3689</sup> *KSR*, 550 U.S. at 418-419.

21 <sup>3690</sup> *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

22 <sup>3691</sup> *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

23 <sup>3692</sup> *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

24 <sup>3693</sup> *Id.* at 88.

<sup>3694</sup> *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

1 Further, a party asserting obviousness in view of a combination of prior art disclosures  
2 must show that a person of ordinary skill in the relevant field had an “apparent reason” to  
3 combine the elements in the manner claimed<sup>3695</sup> and “a reasonable expectation of success.”<sup>3696</sup>

4 For chemical compounds, there must have been a reason both to select the prior art  
5 compound “most promising to modify” and to make the necessary changes to arrive at the  
6 claimed compound.<sup>3697</sup> This protects against the use of hindsight to pick through the prior art  
7 based solely on structural similarity to the claimed compound.<sup>3698</sup> Any assertion of an “apparent  
8 reason” must find a basis in the factual record.<sup>3699</sup>

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11 <sup>3695</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
12 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
13 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
14 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

13 <sup>3696</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
14 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).

15 <sup>3697</sup> *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–  
16 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*  
*Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

17 <sup>3698</sup> *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at \*14. *Accord In re Vaidyanathan*, 381. 985, 994  
18 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.  
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.  
2002).

19 <sup>3699</sup> *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile *KSR* relaxed some of the formalism of earlier decisions  
20 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to  
21 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the  
22 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at  
23 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*  
*invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed  
invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438  
24 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in  
light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that  
defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988”).

1 The “reasonable expectation of success” for a chemical compound must be of all of a  
2 claimed compound’s relevant properties,<sup>3700</sup> including those discovered after the patent was filed  
3 or even issued.<sup>3701</sup> “The basic principle behind this rule is straight-forward—that which would  
4 have been surprising to a person of ordinary skill in a particular art would not have been  
5 obvious.”<sup>3702</sup> Any assertion of a “reasonable expectation of success” must find a basis in the  
6 factual record.<sup>3703</sup>

7 In an obviousness determination, any objective indicia of nonobviousness must be taken  
8 into account.<sup>3704</sup> An objective indicium is any “event[] proved to have actually happened in the  
9 real world” that evidences the nonobvious nature of the invention.<sup>3705</sup> The existence of an  
10 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or  
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12 <sup>3700</sup> *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success  
13 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .  
14 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of  
15 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d  
820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . . Here, the  
ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of  
pharmacological properties that it possesses.”).

16 <sup>3701</sup> *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at  
908.

17 <sup>3702</sup> *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,  
18 such as chemistry, where minor changes in a product or process may yield substantially different results.”).

19 <sup>3703</sup> *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect  
20 inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were  
21 unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general  
22 knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955  
[(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate.  
However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly  
expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re*  
*May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a  
substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

23 <sup>3704</sup> *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

24 <sup>3705</sup> *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

1 surprising results, expressions of skepticism, industry praise, commercial success, and copying  
2 are classical indicia of nonobviousness.<sup>3706</sup> These factual inquiries “guard against slipping into  
3 use of hindsight,”<sup>3707</sup> and “may often be the most probative and cogent evidence of  
4 nonobviousness.”<sup>3708</sup>

5 Also, as with assertions of anticipation, in order for an invention to be obvious, it must  
6 have been fully “in possession” of the public—which requires that the claimed invention have  
7 been enabled.<sup>3709</sup>

8 A element-by-element analysis, identifying each limitation of each asserted claim that is  
9 absent from the prior art, is provided below, and also provided at Exhibit H. The contentions  
10 below are incorporated by reference into Exhibit H, and vice-versa.

11 a) General Overview

12 Defendants fail to provide a single prior art reference that discloses administration of the  
13 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population  
14 ( $\geq 500$  mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,  
15 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying  
16 degrees of purity, in a wide range of doses and administration periods, to subjects who have  
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18 <sup>3706</sup> *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*  
19 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750  
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

20 <sup>3707</sup> *Graham*, 383 U.S. at 36.

21 <sup>3708</sup> *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*  
*Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

22 <sup>3709</sup> *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for  
23 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,  
24 399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for  
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound  
itself is in the possession of the public.”).

1 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance  
2 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo  
3 controlled studies are considered the “gold standard” of clinical studies. Studies involving the  
4 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot  
5 distinguish between the effect of the placebo from that of the active agent. Studies which  
6 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the  
7 independent effects of EPA and DHA.<sup>3710</sup> Inconsistency in dosages and administration periods  
8 and variations in the administered fatty acid compositions also complicate the interpretation of  
9 the results and limit the application of these studies.

10 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with  
11 very high TGs together with patients with high and borderline high TGs indicates that there is no  
12 medical difference in responsiveness to treatment among the groups of people.”<sup>3711</sup> Defendants  
13 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-  
14 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in  
15 patients with high triglycerides ( $\geq 200$  mg/dL and  $< 500$  mg/dL) who were also on statin therapy.  
16 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g  
17 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG  
18 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that  
19 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.<sup>3712</sup> In  
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21 <sup>3710</sup> Mori 2006 at 96.

22 <sup>3711</sup> Defendants’ Joint Invalidity Contentions at 399 (*see* FN 66).

23 <sup>3712</sup> FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6  
24 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been  
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline  
TG values < 500 mg/dL).

1 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were  
2 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use  
3 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a  
4 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the  
5 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to  
6 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.  
7 Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical  
8 difference in responsiveness to treatment between the very-high TG patient population and lower  
9 TG patient populations merely because there was possibly one patient with baseline TG levels of  
10 at least 500 mg/dL.

11 As discussed above in Section III, patients with very-high TG levels were considered  
12 fundamentally different from patients with borderline-high or high TGs from a clinical,  
13 regulatory, and therapeutic perspective.<sup>3713</sup> Clinically, the authoritative guidance to physicians  
14 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III  
15 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;  
16 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients  
17 was atherosclerosis, while the primary risk faced by very-high TG patients was acute  
18 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for  
19 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for  
20 very-high TG patients was TG reduction. This distinction between patients with borderline-  
21 high/high TG levels and patients with very high TG levels is also observed on the regulatory  
22 level. The FDA recognized the different clinical status of the very-high TG population by

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24 <sup>3713</sup> See Bays Jan. 8, 2012 Decl., ¶ 20.

1 approving some drugs specifically for the very-high TG group without granting treatment  
2 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).<sup>3714</sup>

3 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the  
4 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the  
5 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known  
6 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the  
7 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG  
8 level of the patient receiving treatment.

9 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but  
10 increase LDL-C in very-high TG patients.<sup>3715</sup> The fibrate, Tricor (fenofibrate), for example,  
11 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)<sup>3716</sup>  
12 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).<sup>3717</sup> In  
13 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-  
14 significant increase in LDL-C was observed.<sup>3718</sup> In patients with very-high TGs (mean baseline  
15 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).<sup>3719</sup> Similar  
16 results were seen with the administration of Lopid (gemfibrozil).<sup>3720</sup> The differing effects of  
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18 <sup>3714</sup> See Bays Jan. 8, 2012 Decl., ¶ 22.

19 <sup>3715</sup> See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain  
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

20 <sup>3716</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

21 <sup>3717</sup> *Id.*

22 <sup>3718</sup> *Id.* See also, Trilipix Label at 27.

23 <sup>3719</sup> *Id.* See also, Trilipix Label at 27.

24 <sup>3720</sup> See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels  
had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was  
dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while  
subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

1 fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values  
 2 demonstrates how a person of ordinary skill at the time of the invention would have understood  
 3 that one could not simply assume that an observed effect of a TG-lowering agent on lipid  
 4 parameters in patients with normal, borderline-high or high TG levels would be the same in  
 5 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or  
 6 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with  
 7 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-  
 8 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean  
 9 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level  
 10 of 726 mg/dL) experience significantly increased LDL-C levels.

<b>Fibrate</b>	<b>Mean Baseline TG Value</b>	<b>TG</b>	<b>LDL-C</b>	<b>HDL-C</b>	<b>Total-C</b>
Tricor (fenofibrate) <sup>3721</sup>	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

\* = p < 0.05 vs. Placebo

16 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing  
 17 lipid effects depending on the patient's baseline TG level. When administered to patients with  
 18 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-  
 19 C.<sup>3722</sup> It had no significant effect on other lipid-related variable, including LDL-C and Apo-

22 \_\_\_\_\_  
 23 <sup>3721</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 <sup>3722</sup> Chan 2002 I at 2379-81.



1 B.<sup>3723</sup> However, when administered to patients with very-high baseline TG levels, TGs were  
2 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.<sup>3724</sup>  
3 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of  
4 Lovaza/Omacor was beneficial.<sup>3725</sup>

5 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply  
6 assume that a lipid lowering agent would have the same effect in a patient with very-high TG  
7 levels ( $\geq 500$  mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They  
8 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when  
9 the normal, borderline-high or high TG patient populations were administered omega-3 fatty  
10 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was  
11 expected as a natural consequence of lowering TGs. A person of ordinary skill would have  
12 considered the rise in LDL-C to be a direct consequence of TG lowering through increased  
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15 <sup>3723</sup> *Id.*; See also, Westphal at 918.

16 <sup>3724</sup> See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

17 <sup>3725</sup> See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by  $\omega$ -3 fatty acids with lipid transfer*  
18 *activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285,  
19 295 (1999) (“Treatment with  $\omega$ -3 fatty acids appear to change the lipid profile of individuals with elevated TG to  
20 one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity],  
21 serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely  
22 raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic  
23 light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was  
24 substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not  
be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe  
hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the  
long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm  
or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular  
risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty  
acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C  
levels (TC minus HDL-C.)”

1 VLDL particle conversion.<sup>3726</sup> Because normal to high TG patients did not have the large  
2 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not  
3 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree  
4 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,  
5 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the  
6 highest baseline TG levels<sup>3727</sup> and did not increase for patients with lower TG levels. Therefore,  
7 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,  
8 borderline-high or high TG patients was *expected*.

9 Defendants contend that “a composition and its properties are inseparable, and therefore  
10 do not impart any additional patentability,” and that “all of the limitations regarding the  
11 properties of the ethyl EPA compound identified in the claims of the ‘920 patent are inherent to  
12 the compound when administered to a human subject.”<sup>3728</sup> Inherency may not supply a missing  
13 claim limitation in an obviousness analysis unless the inherency would have been obvious to one  
14 of ordinary skill in the art.<sup>3729</sup> Obviousness is based on what is *known* in the art at the time of the  
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17 <sup>3726</sup> Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class  
18 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels  
19 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during  
20 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some  
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the  
decrease in VLDL.”).

21 <sup>3727</sup> Bays 2008 I at 400-402.

22 <sup>3728</sup> Defendants’ Joint Invalidity Contentions at 400.

23 <sup>3729</sup> See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .  
24 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an  
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of  
elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere  
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

1 invention.<sup>3730</sup> It was not known or reasonably expected at the time of the claimed invention that  
2 purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL), would not  
3 substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and  
4 Apo-B necessarily present, or the natural result of the combination of elements explicitly  
5 disclosed by the prior art.<sup>3731</sup> Therefore, inherency does not supply the missing claim elements  
6 in the prior art cited by Defendants.

7 Defendants argue that the claims of the '920 patent which contain "a limiting clause, such  
8 as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively  
9 recited and therefore are not elements.<sup>3732</sup> This is incorrect. "There is nothing inherently wrong  
10 with defining some part of an invention in functional terms."<sup>3733</sup> When a clause "states a  
11 condition that is material to patentability, it cannot be ignored in order to change the substance of  
12 the invention."<sup>3734</sup> The claim term "to effect" acts as a positive limitation if the term represents  
13 "unexpected and improved effects of administration of the claimed compound."<sup>3735</sup> In addition,  
14 the elements represent unexpected and improved effects of administration of purified EPA,  
15 because a person of ordinary skill would not have expected no substantial increase in LDL-C or  
16 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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20 <sup>3730</sup> *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

21 <sup>3731</sup> See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 <sup>3732</sup> Defendants' Joint Invalidity Contentions at 401.

23 <sup>3733</sup> See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 <sup>3734</sup> *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

<sup>3735</sup> *AstraZeneca AB v. Dr. Reddy's Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at \*11-12 (D.N.J. May 18, 2010).

1 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded  
2 patentable weight.

3 b) Identification of Claim Elements Absent from Each Item of Prior  
4 Art

5 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.  
6 Where a limitation is absent from any Independent Claim, that limitation is absent from all  
7 asserted claims, and that analysis is incorporated by reference into each dependent claim. For  
8 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted  
9 claims is not a concession that such limitation is present in the reference. By discussing  
10 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants  
11 have appropriately divided the claim language for any purpose.

12 (1) WO '118

13 WO '118 discloses a composition containing EPA-E for preventing the occurrence of  
14 cardiovascular events in multiple risk patients.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
16 '118 disclose or suggest elements of the '920 Claims. The cited portions of WO '118 do not  
17 disclose or suggest these elements at least because they do not disclose or suggest administration  
18 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
19 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition  
20 with the recited fatty acids compositions or dosage. The cited portions of WO '118 further do  
21 not disclose or suggest a method to effect the recited TG reduction in the subject with the  
22 claimed TG level.

23 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), WO '118  
24 does not disclose or suggest a subject with the recited very high TG levels. WO '118 also does

1 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions or dosage. WO '118 further does not disclose or suggest a method to effect the  
3 recited TG reduction in the subject with the claimed TG level.

4 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
5 having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to  
6 disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With  
7 respect to Claim 8, this reference fails to disclose or suggest the recited reduction in  
8 Apolipoprotein B in the subject with the claimed TG level. With respect to Claim 9, this  
9 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the  
10 claimed TG level.

11 (2) WO '900

12 WO '900 describes methods for obtaining EPA-rich compositions.

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
14 '900 disclose or suggest elements of the '920 Claims. The cited portions of WO '900 do not  
15 disclose or suggest these elements at least because they do not disclose or suggest administration  
16 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
17 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition  
18 with the recited fatty acid dosage or administration period. The cited portions of WO '900  
19 further do not disclose or suggest a method to effect the recited TG reduction in the subject with  
20 the claimed TG level.

21 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), WO '900  
22 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does  
23 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
24

1 dosage or administration period. WO '900 further does not disclose or suggest a method to  
2 effect the recited TG reduction in the subject with the claimed TG level.

3 Further, with respect to Claim 2, this reference does not disclose or suggest  
4 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
5 disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim  
6 5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels.  
7 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in  
8 TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to  
9 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
10 level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in  
11 VLDL-C in the subject with the claimed TG level.

12 (3) Contacos

13 Contacos describes a study designed to determine the safety and efficacy of a statin  
14 (pravastatin) combined with fish oil either alone or in combination, for the management of  
15 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in  
16 the claims.

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
18 Contacos disclose or suggest elements of the '920 Claims. The cited portions of Contacos do not  
19 disclose or suggest these elements at least because they do not disclose or suggest administration  
20 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
21 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition  
22 with the recited fatty acid compositions, dosage, or administration period. The cited portions of  
23 Contacos further do not disclose or suggest a method of administering the claimed  
24 pharmaceutical composition to effect the recited TG reduction.

1 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Contacos  
2 does not disclose or suggest a subject with the recited very high TG level. Contacos also does  
3 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
4 compositions, dosage, or administration period. Contacos further does not disclose or suggest a  
5 method of administering the claimed pharmaceutical composition to effect the recited TG  
6 reduction.

7 Further, with respect to Claim 2, this reference does not disclose or suggest  
8 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
9 disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims  
10 6 and 7, this reference fails to disclose or suggest the administration of the claimed  
11 pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this  
12 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
13 composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this  
14 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
15 composition to effect the recited reduction in VLDL-C.

16 (4) Grimsgaard

17 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design  
18 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,  
19 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG  
20 levels.

21 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
22 Grimsgaard disclose or suggest elements of '920 Claims. The cited portions of Grimsgaard do  
23 not disclose or suggest these elements at least because they do not disclose or suggest  
24 administration of EPA with the recited purity to a subject with the recited very high TG levels.

1 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical  
2 composition with the recited fatty acid compositions or administration period. The cited portions  
3 of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction in  
4 the subject with the claimed TG level.

5 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Grimsgaard  
6 does not disclose or suggest a subject with the recited very high TG levels. Grimsgaard also  
7 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
8 compositions or administration period. Grimsgaard further does not disclose or suggest a  
9 method to effect the recited TG reduction in the subject with the claimed TG level.

10 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
11 having the recited baseline LDL-C levels. With respect to Claim 7, this reference fails to  
12 disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With  
13 respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
14 the subject with the claimed TG level.

15 (5) Hayashi

16 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for  
17 8 weeks. The purity of the composition is not reported. The study was not placebo controlled  
18 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride  
19 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220  
20 mg/dl.

21 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the  
22 '920 patent claims. For example, the cited portions of Hayashi do not disclose or suggest  
23 administration of EPA with the recited purity to a subject with the recited very high TG levels  
24 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject



1 had a TG level above 400 mg/dl. The cited portions of Hayashi further do not disclose or  
2 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or  
3 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the  
4 recited TG reduction without substantially increasing LDL-C in a subject with the recited very  
5 high TG levels.

6 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Hayashi  
7 does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not  
8 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or dosage. Hayashi further does not disclose or suggest a method to effect the  
10 recited TG reduction in the subject with the claimed TG level.

11 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
12 having the recited baseline LDL-C levels. With respect to Claims 8, this reference fails to  
13 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
14 level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in  
15 VLDL-C in the subject with the claimed TG level.

16 (6) Katayama

17 Katayama was directed to an investigation of the safety and efficacy of Epadel during  
18 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,  
19 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and  
20 was not placebo controlled.

21 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
22 Katayama disclose or suggest elements of the '920 Claims. The cited portions of Katayama do  
23 not disclose or suggest these elements at least because they do not disclose or suggest  
24 administration of EPA with the recited purity to a subject with the recited very high TG levels.

1 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical  
2 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama  
3 further do not disclose or suggest a method to effect the recited TG reduction in the subject with  
4 the claimed TG level.

5 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Katayama  
6 does not disclose or suggest a subject with the recited very high TG level. Katayama also does  
7 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
8 compositions or dosage. Katayama further does not disclose or suggest a method to effect the  
9 recited TG reduction in the subject with the claimed TG level.

10 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
11 having the recited baseline LDL-C levels. With respect to Claims 8, this reference fails to  
12 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
13 level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in  
14 VLDL-C in the subject with the claimed TG level.

15 (7) Leigh-Firbank

16 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle  
17 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank  
18 does not administer EPA of the purity recited in the claims.

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
20 Leigh-Firbank disclose or suggest elements of the '920 Claims. The cited portions of Leigh-  
21 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest  
22 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
23 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed  
24 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration

1 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of  
2 administering the claimed pharmaceutical composition to effect the recited TG reduction.

3 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Leigh-  
4 Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-  
5 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the  
6 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not  
7 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
8 the recited TG reduction.

9 Further, with respect to Claim 2, this reference does not disclose or suggest  
10 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference does  
11 not disclose or suggest the subject having the recited baseline LDL-C level. With respect to  
12 Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed  
13 pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this  
14 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
15 composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this  
16 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
17 composition to effect the recited reduction in VLDL-C.

18 (8) Lovaza PDR

19 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

20 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
21 Lovaza PDR disclose or suggest elements of the '920 Claims. The cited portions of the Lovaza  
22 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
23 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
24 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed

1 pharmaceutical composition with the recited fatty acid compositions or administration period.  
2 The cited portions of the Lovaza PDR further do not disclose or suggest a method of  
3 administering the claimed pharmaceutical composition to effect the recited TG reduction.

4 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), the Lovaza  
5 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
6 acid compositions or administration period. The Lovaza PDR further does not disclose or  
7 suggest a method of administering the claimed pharmaceutical composition to effect the recited  
8 TG reduction.

9 Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the  
10 administration of the claimed pharmaceutical composition to effect the recited reduction in TG.

11 With respect to Claims 8, this reference fails to disclose or suggest the administration of the  
12 claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With  
13 respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed  
14 pharmaceutical composition to effect the recited reduction in VLDL-C.

15 (9) Maki

16 Maki administered 1.52g/day DHA supplements to patients with below-average levels of  
17 HDL-C. Maki does not administer EPA of the purity recited in the claims.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki  
19 disclose or suggest elements of the '920 Claims. The cited portions of Maki do not disclose or  
20 suggest these elements at least because they do not disclose or suggest administration of EPA  
21 with the recited purity to a subject with the recited very high TG level. The cited portions of  
22 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited  
23 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do  
24

1 not disclose or suggest a method of administering the claimed pharmaceutical composition to  
2 effect the recited TG reduction.

3 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Maki does  
4 not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose  
5 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,  
6 dosage, or administration period. Maki further does not disclose or suggest a method of  
7 administering the claimed pharmaceutical composition to effect the recited TG reduction.

8 With respect to Claim 2, this reference does not disclose or suggest administration of the  
9 claimed pharmaceutical composition to the subject 1 to 4 times per day. With respect to Claim  
10 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels.  
11 With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of  
12 the claimed pharmaceutical composition to effect the recited reduction in TG. With respect to  
13 Claims 8, this reference fails to disclose or suggest the administration of the claimed  
14 pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to  
15 Claims 9, this reference fails to disclose or suggest the administration of the claimed  
16 pharmaceutical composition to effect the recited reduction in VLDL-C.

17 (10) Matsuzawa

18 Matsuzawa administered Epadel ® to patients with hyperlipaemia in order to study its  
19 long-term use in the treatment of the disease and was not placebo controlled.

20 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
21 Matsuzawa disclose or suggest elements of the '920 Claims. The cited portions of Matsuzawa  
22 do not disclose or suggest these elements at least because they do not disclose or suggest  
23 administration of EPA with the recited purity to a subject with the recited very high TG level.  
24 The cited portions of Matsuzawa do not disclose or suggest these elements at least because they

1 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions, dosage, or administration period. The cited portions of Matsuzawa further do not  
3 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
4 the recited TG reduction in the subject with the claimed TG level.

5 With respect to Claims 1 of the '920 Patent (and therefore all asserted claims),  
6 Matsuzawa does not disclose or suggest the claimed pharmaceutical composition with the recited  
7 fatty acid compositions, dosage, or administration period. Matsuzawa further does not disclose  
8 or suggest a method of administering the claimed pharmaceutical composition to effect the  
9 recited TG reduction in the subject with the claimed TG level.

10 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
11 having the recited baseline LDL-C levels. With respect to Claim 7, this reference fails to  
12 disclose or suggest the administration of the claimed pharmaceutical composition to effect the  
13 recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this  
14 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
15 composition to effect the recited reduction in Apolipoprotein B in the subject with the claimed  
16 TG level. With respect to Claims 9, this reference fails to disclose or suggest the administration  
17 of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the  
18 subject with the claimed TG level.

19 (11) Mori 2000

20 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum  
21 lipids and lipoproteins, glucose and insulin in humans.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
23 2000 disclose or suggest elements of Claims XX. The cited portions of Mori 2000 do not  
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
2 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition  
3 with the recited fatty acid compositions or administration period. The cited portions of Mori  
4 2000 further do not disclose or suggest a method to effect the recited TG reduction in the subject  
5 with the claimed TG level.

6 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Mori 2000  
7 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 further  
8 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or administration period. Mori 2000 further does not disclose or suggest a method  
10 to effect the recited TG reduction in the subject with the claimed TG level.

11 Further, with respect to Claim 2, this reference does not disclose or suggest  
12 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
13 disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim  
14 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the  
15 claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited  
16 reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims  
17 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with  
18 the claimed TG level.

19 (12) Mori 2006

20 Mori 2006 is a review which reports data from clinical trials which compared the  
21 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
23 2006 disclose or suggest elements of the '920 Claims. The cited portions of Mori 2006 do not  
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG level. The cited  
2 portions of Mori 2006 further do not disclose or suggest administration of the claimed  
3 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration  
4 period to the subject with the claimed TG level. The cited portions of Mori 2006 further do not  
5 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed  
6 TG level.

7 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Mori 2006  
8 does not disclose or suggest a subject with the recited very high TG levels who does not receive  
9 concurrent lipid altering therapy. Mori 2006 also does not disclose or suggest administration of  
10 the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or  
11 administration period to the subject with the claimed TG level. Mori 2006 further does not  
12 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed  
13 TG level.

14 Further, with respect to Claim 2, this reference does not disclose or suggest  
15 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
16 disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim  
17 5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels.  
18 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in  
19 TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to  
20 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
21 level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in  
22 VLDL-C in the subject with the claimed TG level.



1 (13) Nozaki

2 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The  
3 purity of the composition is reported as 90%. The study was not placebo controlled and was  
4 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165  
5 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG  
6 patient population.

7 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the  
8 '920 patent claims. For example, the cited portions of Nozaki do not disclose or suggest  
9 administration of EPA with the recited purity to a subject with the recited very high TG levels  
10 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do  
11 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
12 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a  
13 method to effect the recited TG reduction without substantially increasing LDL-C in a subject  
14 with the recited very high TG levels.

15 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the  
16 '920 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least  
17 because they do not disclose or suggest administration of EPA with the recited purity to a subject  
18 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The  
19 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical  
20 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki  
21 further do not disclose or suggest a method to effect the recited TG reduction without  
22 substantially increasing LDL-C.

23 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Nozaki  
24 does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not

1 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions or dosage. Nozaki further does not disclose or suggest a method to effect the  
3 recited TG reduction in the subject with the claimed TG level.

4 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
5 having the recited baseline LDL-C levels. With respect to Claims 8, this reference fails to  
6 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
7 level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in  
8 VLDL-C in the subject with the claimed TG level.

9 (14) Omacor PDR

10 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
12 Omacor PDR disclose or suggest elements of the '920 Claims. The cited portions of the Omacor  
13 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
14 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
15 The cited portions of the Omacor PDR further do not disclose or suggest the claimed  
16 pharmaceutical composition with the recited fatty acid compositions or administration period.  
17 The cited portions of the Omacor PDR further do not disclose or suggest a method of  
18 administering the claimed pharmaceutical composition to effect the recited TG reduction.

19 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), the Omacor  
20 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
21 acid compositions or administration period. The Omacor PDR further does not disclose or  
22 suggest a method of administering the claimed pharmaceutical composition to effect the recited  
23 TG reduction.

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1 Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the  
2 administration of the claimed pharmaceutical composition to effect the recited reduction in TG.  
3 With respect to Claims 8, this reference fails to disclose or suggest the administration of the  
4 claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With  
5 respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed  
6 pharmaceutical composition to effect the recited reduction in VLDL-C.

7 (15) Satoh

8 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
9 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
10 systemic inflammation.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
12 Satoh disclose or suggest elements of the '920 Claims. The cited portions of Satoh do not  
13 disclose or suggest these elements at least because they do not disclose or suggest administration  
14 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
15 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with  
16 the recited fatty acid dosage. The cited portions of Satoh further do not disclose or suggest a  
17 method to effect the recited TG reduction in the subject with the claimed TG level.

18 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Satoh does  
19 not disclose or suggest a subject with the recited very high TG level. Satoh also does not  
20 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage.  
21 Satoh further does not disclose or suggest a method to effect the recited TG reduction in the  
22 subject with the claimed TG level.

23 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
24 having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to

1 disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With  
2 respect to Claims 8, this reference fails to disclose or suggest the recited reduction in  
3 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this  
4 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the  
5 claimed TG level.

6 (16) Shinozaki

7 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and  
8 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
10 Shinozaki disclose or suggest elements of the '920 Claims. The cited portions of Shinozaki do  
11 not disclose or suggest these elements at least because they do not disclose or suggest  
12 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
13 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical  
14 composition with the recited fatty acid dosage. The cited portions of Shinozaki further do not  
15 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed  
16 TG level.

17 With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Shinozaki  
18 does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does  
19 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
20 dosage. Shinozaki further does not disclose or suggest a method to effect the recited TG  
21 reduction in the subject with the claimed TG level.

22 Further, with respect to Claim 2, this reference does not disclose or suggest  
23 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to  
24 disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim

1 5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels.  
2 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in  
3 TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to  
4 disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG  
5 level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in  
6 VLDL-C in the subject with the claimed TG level.

7 (17) Takaku

8 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-  
9 term use and was not placebo controlled.

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
11 Takaku disclose or suggest elements of the '920 Claims. The cited portions of Takaku do not  
12 disclose or suggest these elements at least because they do not disclose or suggest administration  
13 of EPA with the recited purity to a subject with the recited very high TG level. The cited  
14 portions of Takaku do not disclose or suggest these elements at least because they do not disclose  
15 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,  
16 dosage, or administration period. The cited portions of Takaku further do not disclose or suggest  
17 a method of administering the claimed pharmaceutical composition to effect the recited TG  
18 reduction in the subject with the claimed TG level.

19 With respect to Claims 1 of the '920 Patent (and therefore all asserted claims), Takaku  
20 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
21 compositions, dosage, or administration period. Takaku further does not disclose or suggest a  
22 method of administering the claimed pharmaceutical composition to effect the recited TG  
23 reduction in the subject with the claimed TG level.

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1 Further, with respect to Claim 4, this reference fails to disclose or suggest the subject  
2 having the recited baseline LDL-C levels. With respect to Claim 5, this reference fails to  
3 disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 6  
4 and 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with  
5 the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the  
6 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
7 Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the  
8 subject with the claimed TG level.

9 c) The Prior Art Does Not Render the Claims Obvious

10 Defendants have not identified by clear and convincing evidence that the asserted claims  
11 of the '920 patent would have been *prima facie* obvious in light of the references cited, either  
12 alone or in combination. As described above, none of the references discloses all of the elements  
13 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without  
14 explanation, and argue they somehow must be combined to render obvious the asserted claims.  
15 Where Defendants have failed to make disclosures with the specificity required by Local Patent  
16 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the  
17 claim elements at issue.

18 Facts supporting the non-obviousness of the claims of the '920 patent are discussed in  
19 detail below. The objective indicia discussed in Section V.O further demonstrate that the '920  
20 patent is not obvious. In short, Defendants have not met their burden of showing that the claims  
21 would have been obvious.

22 (1) Defendants Do Not Demonstrate that the Independent  
23 Claims of the '920 patent Would Have Been Obvious

24 (a) Defendants Do Not Demonstrate that a Person of  
Ordinary Skill in the Art Would Have Had Any

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Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

- (i) The '920 patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, Further in View of Nozaki and/or Hayashi and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '920 patent, Defendants present a combination of seven references:

“the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi and further in view of Leigh-Firbank and/or Mori 2000.”<sup>3736</sup> Defendants also present charts purporting to assert that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 61 separate references, they additionally do not identify any motivation for combining these references.<sup>3737, 3738</sup> Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent

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<sup>3736</sup> Defendants' Joint Invalidation Contentions at 379.

<sup>3737</sup> Defendants' bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as described in the references cited above in Section V.B.2) in view of, at least, the references cited in V.B.3. and 4., including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald” similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidation Contentions at 394.

<sup>3738</sup> Defendants' bare assertion that “the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,” and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure requirements of the Nevada Local Patent Rules. *See* Defendants' Joint Invalidation Contentions at 392-93.

1 reason” to combine must find a basis in the factual record.<sup>3739</sup> Defendants’ unsupported cobbling  
2 of selective disclosures represents hindsight reconstruction.<sup>3740</sup> Defendants’ contentions are no  
3 more than an assertion that certain claim elements were known in the prior art. Throughout their  
4 contentions, Defendants’ selectively cite to data points in a reference without considering other  
5 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
6 that it teaches.<sup>3741</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
7 obviousness.

8 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
9 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed  
10 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a  
11 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the  
12 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a  
13 significant increase in LDL-C levels in the very high TG patient population, for whom the  
14 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,  
15

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16 <sup>3739</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3740</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>3741</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)



1 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce  
2 TG levels in adult patients with very-high ( $\geq 500$  mg/dL) TG levels.

3 The proposed combinations do not render the independent claims of the '920 patent  
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
5 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza  
6 package insert specifically) during prosecution.<sup>3742</sup>

7 The analysis of the independent claim of the '920 patent is incorporated into all asserted  
8 claims that depend from that claim.

9 (a) A Person of Ordinary Skill Would  
10 Not Have Been Motivated to  
11 Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with Pure EPA

12 For an invention to be obvious, there must have been an "apparent reason" to make it.  
13 The subject matter of the '920 patent claims would not have been obvious in light of these  
14 references because a person of ordinary skill would not have been motivated to purify EPA or  
15 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
16 levels without an increase in LDL-C levels.

17 (i) Katayama and/or Matsuzawa  
18 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

19 Both Katayama and Matsuzawa are long term studies directed to an investigation of the  
20 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies

21  
22 <sup>3742</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the  
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
24 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").

1 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may  
2 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the  
3 art would not and could not attribute any observed effect (and the magnitude of that effect) to  
4 that of the drug. Any observed effect could be placebo dependent.<sup>3743</sup> As discussed above in  
5 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with  
6 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG  
7 patients because patients with higher TG levels had different lipid responses compared to  
8 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally  
9 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical  
10 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary  
11 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were  
12 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art  
13 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-  
14 high or high TG patients, was expected. At the priority date of the ‘920 patent, a person of  
15 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients  
16 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been  
17 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG  
18 lowering through increased VLDL particle conversion.

19 Defendants argue that these studies disclose known “clinical benefits” of administering  
20 pure EPA, lowering triglycerides without raising LDL-C.<sup>3744</sup> This is an incorrect characterization  
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22 <sup>3743</sup>See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a  
23 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a  
24 placebo-controlled study and why results compared only to baseline may be misleading.)

<sup>3744</sup> Defendants’ Joint Invalidity Contentions at 394-95.

1 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of  
2 long term treatment of Epedel and its ability to lower both serum total cholesterol and TG levels.  
3 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.  
4 Defendants’ selective citation of LDL-C data from these references represents the improper use  
5 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and  
6 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw  
7 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C  
8 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the  
9 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.<sup>3745</sup> The  
10 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor  
11 would a person of ordinary skill view these references as teaching such a benefit for very-high  
12 TG patients.

13 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid  
14 effects. These studies fail to provide a head to head comparison of EPA versus DHA.  
15 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to  
16 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

17 In addition, Katayama and Matsuzawa do not disclose the purity of the Epedel used. The  
18 purity of Epedel has varied over time and across different formulations of the product, therefore  
19 it is difficult to determine the purity of the version of Epedel used unless it is specified by the  
20 disclosure. One cannot simply rely on the fact that Epedel was administered and assume that the  
21 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and  
22 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference  
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24 <sup>3745</sup> Defendants’ Joint Invalidity Contentions at 394-95.

1 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.  
2 Nishikawa,<sup>3746</sup> published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.  
3 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite  
4 purity.<sup>3747</sup>

5 Further, Katayama and Matsuzawa were small studies conducted in only Japanese  
6 patients. These studies would not have been extrapolated to Western populations because the  
7 Japanese diet contains much more fish and has a number of other different attributes. The  
8 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In  
9 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where  
10 the patient population is exclusively Japanese cannot be generalized to other populations.<sup>3748</sup>  
11 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical  
12 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-  
13 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand  
14 that the Japanese respond differently to lipid lowering agents than Westerners.

15 Defendants rely on Katayama to demonstrate the "known clinical benefits of  
16 administering pure EPA - lowering triglycerides without raising LDL-C."<sup>3749</sup> However,  
17 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term  
18 treatment in patients with hyperlipidemia.<sup>3750</sup> Katayama does not disclose *any* LDL-C related

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20 <sup>3746</sup> Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI<sub>2</sub> and PGI<sub>3</sub> Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

21 <sup>3747</sup> See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

22 <sup>3748</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

23 <sup>3749</sup> Defendants' Joint Invalidity Contentions at 395 and 396.

24 <sup>3750</sup> Katayama at 2.

1 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that  
2 reference to provide any such disclosure. The only results disclosed by Katayama were a  
3 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was  
4 administered to patients with borderline-high to high TG levels, and its safety for long term use  
5 in this patient population.<sup>3751</sup> In addition to Katayama’s lack of disclosure regarding LDL-C,  
6 Defendants identify no other basis upon which a person of ordinary skill would have sought to  
7 combine the composition disclosed in Katayama with the Lovaza PDR.

8 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of  
9 administering pure EPA - lowering triglycerides without raising LDL-C.”<sup>3752</sup> However,  
10 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall  
11 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of  
12 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13  
13 were evaluated for improvement in serum triglycerides levels.<sup>3753</sup> It is unclear which of the 26  
14 patients were included in each separate evaluation; therefore one cannot determine the baseline  
15 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack  
16 of a placebo control makes it less likely that the results of this study can be generalized as an  
17 effect on any population as a whole and provides no insight with respect to the very-high TG  
18 patient population.

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22 <sup>3751</sup> *Id.* at 16.

23 <sup>3752</sup> Defendants’ Joint Invalidation Contentions at 394 and 395.

24 <sup>3753</sup> Matsuzawa at 7 and 19.

1 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,  
2 and one participant with TG levels > 1,000 mg/dL.<sup>3754</sup> However, when analyzing the lipid  
3 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL  
4 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess  
5 triglyceride levels.”<sup>3755</sup> Fig. 4, which depicts the changes in serum triglycerides, shows that the  
6 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500  
7 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than  
8 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of  
9 undisclosed purity). The identification of three patients with TG levels between 400 and less  
10 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of  
11 ordinary skill would not understand that the reference makes any such disclosure. As discussed  
12 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG  
13 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no  
14 evidence to the contrary.

15 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a  
16 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.<sup>3756</sup> The disclosure  
17 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were  
18 excluded from the LDL-C results because the Friedewald’s Equation was used to calculate LDL-  
19 C levels. The Friedewald’s Equation cannot be used for patients with triglyceride levels of at  
20 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

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22 <sup>3754</sup> *Id.* at 23.

23 <sup>3755</sup> *Id.* at 10.

24 <sup>3756</sup> *Id.* at 11.

1 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of  
2 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary  
3 skill in the art, however, would have expected the same treatment in patients with very high TG  
4 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that  
5 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered  
6 triglyceride levels.<sup>3757</sup> At best, Matsuzawa demonstrates the uncertainty and confusion related to  
7 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify  
8 any other basis upon which a person of ordinary skill would have sought to combine the  
9 composition disclosed in Matsuzawa with the Lovaza PDR.

10 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that  
11 compositions comprising EPA as recited in the asserted claims lowers triglycerides without  
12 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA  
13 increases LDL-C.<sup>3758</sup> Defendants identify no other basis upon which a person of ordinary skill  
14 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank  
15 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the  
16 asserted claims of the '920 patent.

17 (ii) Nozaki and/or Hayashi  
18 Would Not Have Rendered  
19 the Asserted Claims Obvious

20 Defendants contend that the asserted claims of the '920 patent would have been obvious  
21 in view Nozaki and/or Hayashi in combination with other references, but they do not explain

22 <sup>3757</sup> *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA  
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific  
24 compositions used, or identify the patient populations were observed.

<sup>3758</sup> *See, e.g.,* Rambjor.

1 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
2 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
3 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
4 very high TG patient population.

5 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
6 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
7 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
8 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
9 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
10 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
11 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
12 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
13 patient population were abnormally high and would not have relied upon these results. Further,  
14 the person of skill in the art would not have looked to this patient population to predict the Apo-  
15 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
16 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
17 levels.<sup>3759</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
18 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
19 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
20 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
21 to the very high TG patient population.

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<sup>3759</sup> Nozaki at 256.



1 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
2 the EPA and the DHA content in the composition that was administered is unknown. A person  
3 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
4 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
5 C were not statistically significant.<sup>3760</sup> Further, the person of skill in the art would not have  
6 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
7 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
8 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
9 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
10 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
11 administered to the very high TG patient population.

12 Further, Hayashi was a small study conducted in only Japanese patients and was not  
13 placebo controlled. This study would not have been extrapolated to Western populations  
14 because the Japanese diet contains much more fish and has a number of other different attributes.  
15 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
16 populations. In fact, Defendants' own reference states that the results from studies where the  
17 patient population is exclusively Japanese cannot be generalized to other populations.<sup>3761</sup> The  
18 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
19 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
20 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
21 the Japanese respond differently to lipid lowering agents than Westerners.

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23 <sup>3760</sup> Hayashi at 26, Table I.

24 <sup>3761</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 Further, Defendants have failed to offer a purported combination of references as part of  
2 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
3 motivation to combine Nozaki and Hayashi with the other references of their purported  
4 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
5 references.

6 (iii) Leigh-Firbank and/or Mori  
7 2000 Do Not Disclose  
8 Purported Knowledge that  
9 DHA was Responsible for the  
10 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
11 C levels.”<sup>3762</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
13 rely upon to support this statement does not categorize the increase in LDL-C as a “negative  
14 effect” in light of the overall impact of the disclosed composition on all lipid parameters.  
15 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As  
16 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
17 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—  
18 as in very-high TG patients because patients with higher TG levels had different lipid responses  
19 compared to patients with lower TG levels. Patients with very-high TG levels were considered  
20 fundamentally different from patients with borderline-high or high triglycerides from a lipid  
21 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person  
22 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)

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24 <sup>3762</sup> Defendants’ Joint Invalidity Contentions at 398.

1 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but  
2 would substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was  
4 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,  
5 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride  
6 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either  
7 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A  
8 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any  
9 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the  
10 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)  
11 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated  
12 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA  
13 and DHA.<sup>3763</sup> A person of ordinary skill would understand that studies directed to EPA and  
14 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on  
15 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-  
16 Firbank, because purified EPA and DHA were not administered separately.

17 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent  
18 effects of EPA and DHA individually, even though it administered a combination of EPA and  
19 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions  
20 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet  
21 phospholipid EPA were *independently* associated with the decrease in fasting TGs,<sup>3764</sup> and DHA

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23 <sup>3763</sup> Mori 2006 at 96.

24 <sup>3764</sup> Leigh-Firbank at 440.

1 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state  
2 of the art and numerous publications cited by Defendants.<sup>3765</sup> It is widely accepted that DHA  
3 also has a hypotriglyceridemic effect.

4 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients  
5 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-  
6 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching  
7 away from the claimed invention. “A reference may be said to teach away when a person of  
8 ordinary skill, upon [examining] the reference, would be discouraged from following the path set  
9 out in the reference, or would be led in a direction divergent from the path that was taken by the  
10 applicant.”<sup>3766</sup> Although teaching away is fact-dependent, “in general, a reference will teach  
11 away if it suggests that the line of development flowing from the reference’s disclosures is  
12 unlikely to be productive of the result sought by the applicant.”<sup>3767</sup>

13 Mori 2000 concludes that the changes effected by DHA supplementation “may represent  
14 a more favorable lipid profile than after EPA supplementation.”<sup>3768</sup> For example, it states that  
15 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL  
16 cholesterol and a significant increase in the HDL<sub>2</sub>-cholesterol subfraction, without adverse  
17 effects on fasting glucose concentrations.”<sup>3769</sup> Mori 2000 also states that “[d]espite an increase  
18 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may

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19 <sup>3765</sup> See, e.g. Grimsgaard at 654.

20 <sup>3766</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

21 <sup>3767</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354  
22 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)  
23 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

23 <sup>3768</sup> Mori 2000 at 1092.

24 <sup>3769</sup> Mori 2000 at 1088.

1 be favorable.”<sup>3770</sup> Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori  
2 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the  
3 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away  
4 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for  
5 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,  
6 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration  
7 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,  
8 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
9 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill  
10 would have sought to combine Mori 2000 with the Lovaza PDR.

11 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
12 was known that DHA alone was responsible for the increase in LDL-C levels. Further,  
13 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
14 has little effect on LDL-C levels.<sup>3771</sup> Defendants identify no other basis upon which a person of  
15 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,  
16 Leigh-Firbank and/or Mori 2000.

- 17 (ii) The ‘920 patent is not Obvious Over the  
18 Omacor PDR/Lovaza PDR, in Combination  
19 with Katayama and/or Matsuzawa, and/or  
20 Takaku, Further in View of Nozaki and/or  
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23 <sup>3770</sup> Mori 2000 at 1092.

24 <sup>3771</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '920 patent, Defendants present a combination of nine references:

“the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki.”<sup>3772</sup>

Defendants also present charts purporting to assert that an additional 58 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 58 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>3773</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>3774</sup> Defendants’ contentions are no more than an assertion that certain

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<sup>3772</sup> Defendants’ Joint Invalidity Contentions at 395.

<sup>3773</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3774</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 claim elements were known in the prior art. Throughout their contentions, Defendants’  
2 selectively cite to data points in a reference without considering other disclosures or even the  
3 reference as a whole. Each reference, however, must be evaluated for all that it teaches.<sup>3775</sup>  
4 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method  
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the  
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR  
8 further do not disclose a method to effect the claimed TG reduction without substantially  
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA  
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the  
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose  
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375  
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500  
14 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’920  
15 patent obvious and Defendants’ burden to prove otherwise is especially difficult because the  
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both  
17 generally and the Lovaza package insert specifically) during prosecution.<sup>3776</sup>

18 The analysis of the independent claims of the ’920 patent is incorporated into all asserted  
19 claims that depend from those Claims.

20 (a) A Person of Ordinary Skill Would  
21 Not Have Been Motivated to

22 <sup>3775</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>3776</sup> *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

3 For an invention to be obvious, there must have been an “apparent reason” to make it.  
4 The subject matter of the ‘920 patent claims would not have been obvious in light of these  
5 references because a person of ordinary skill would not have been motivated to purify EPA or  
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
7 levels without an increase in LDL-C levels.

8 (i) Grimsgaard, Katayama,  
9 Matsuzawa and/or Takaku  
10 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

11 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the  
12 “known clinical benefits of administering pure EPA - lowering triglycerides without raising  
13 LDL-C.” As discussed in Section V.H.3.c.1.a.i.a.i, incorporated herein by reference, Katayama  
14 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to  
15 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported  
16 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that  
17 the LDL-C results obtained were a clinical benefit.

18 Defendants also rely on Grimsgaard to support their assertion that “administration of  
19 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”<sup>3777</sup> However,  
20 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on  
21 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

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<sup>3777</sup> Defendants’ Joint Invalidity Contentions at 398.



1 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA  
2 administered to people with normal triglyceride levels for 7 weeks.<sup>3778</sup> The results from the  
3 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the  
4 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that  
5 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid  
6 supplements, which is consistent with previous studies which “suggested that serum HDL-C is  
7 better maintained with oil rich in DHA than oil rich in EPA.”<sup>3779</sup> Although Grimsgaard states  
8 that EPA may produce a small decrease in serum total cholesterol, it does not specifically  
9 comment on EPA’s effect on LDL-C.

10 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to  
11 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in  
12 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-  
13 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”<sup>3780</sup> The  
14 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the  
15 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s  
16 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to  
17 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s  
18 disclosure highlights the importance of a placebo-controlled study and why results compared  
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22 <sup>3778</sup> Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG  
levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG  
levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

23 <sup>3779</sup> Grimsgaard at 654.

24 <sup>3780</sup> Defendants’ Joint Invalidation Contentions at 398 (see FN 63).

only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

TABLE 4  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>2</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>2</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>4</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>5</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>3-5</sup> One-sample t test of difference between baseline and 7 wk: <sup>3</sup> P < 0.001, <sup>4</sup> P < 0.01, <sup>5</sup> P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”<sup>3781</sup> However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements.”<sup>3782</sup> Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that

<sup>3781</sup> Grimsgaard at 657.

<sup>3782</sup> Grimsgaard at 654.

1 | it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did  
2 | not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and  
3 | proposed combinations of prior art. Defendants point to a non-significant increase in DHA and  
4 | non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified  
5 | DHA results in increased LDL-C levels while administration of purified EPA resulted in a  
6 | decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did  
7 | not have statistically significantly effects on LDL-C compared to placebo.<sup>3783</sup> A person of  
8 | ordinary skill would not draw conclusions regarding differences between EPA and DHA based  
9 | on statistically insignificant results.

10 | Defendants also rely on Takaku to support their assertion that “clinical benefits of  
11 | administering purified EPA—lowering triglycerides without raising LDL-C” was known in the  
12 | art.<sup>3784</sup> Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and  
13 | safety of Epadel (of undisclosed purity)<sup>3785</sup> based on long-term administration.<sup>3786</sup>

14 | A person of ordinary skill would not have concluded based on Takaku that EPA lowers  
15 | triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly  
16 | acknowledges that “only a few subjects were examined” and cautions against drawing a  
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18 | <sup>3783</sup>In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a  
19 | statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to  
20 | interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have  
21 | argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make  
22 | such arguments for the obvious reason that it does not support their argument that EPA was known to have little or  
23 | no impact on LDL-C levels.

21 | <sup>3784</sup> Defendants’ Joint Invalidity Contentions at 395.

22 | <sup>3785</sup> It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by  
23 | the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),  
24 | Nakamura at 23 (Epadel with purity > 90%).

24 | <sup>3786</sup> Takaku at ICOSAPENT\_DFNDT00006834.

1 conclusion “only from the results of the present study.”<sup>3787</sup> Because the study did not include  
2 any placebo control, a person of ordinary skill in the art would understand these reports do not  
3 provide the ability to conclude that the observed lipid effects would have occurred independent  
4 of the drug that is administered. In addition, the study was conducted exclusively in Japanese  
5 patients, and a person of ordinary skill would not have expected the results to be applicable to the  
6 general population.<sup>3788</sup>

7 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a  
8 person of ordinary skill would not have expected the results to be applicable to patients with  
9 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because  
10 measurement was not feasible due to “insufficient sample.”<sup>3789</sup> It is possible that patients with  
11 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in  
12 calculating LDL-C levels when triglyceride level is above 400 mg/dL.<sup>3790</sup> Moreover, the study  
13 does not provide different LDL-C graphs based on the baseline triglyceride levels.<sup>3791</sup> Therefore,  
14 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had  
15 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C  
16 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile  
17 throughout the study period, decreasing slightly at times but increasing by more than 8% at other  
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<sup>3787</sup> Takaku at ICOSAPENT\_DFNDT00006897.

21 <sup>3788</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.”)

22 <sup>3789</sup> Takaku at ICOSAPENT\_DFNDT00006884.

23 <sup>3790</sup> See Matsuzawa at ICOSPENT\_DFNDTS00006450.

24 <sup>3791</sup> Takaku at Fig. 13, ICOSAPENT\_DFNDT00006882.

1 times.<sup>3792</sup> Because of this volatility, a person of ordinary skill would not be able to conclude  
2 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in  
3 LDL-C, stating only that the fluctuation in LDL-C was not significant.<sup>3793</sup>

4 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA  
5 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has  
6 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the  
7 administration of *fish oil* to hypercholesterolemia patients.”<sup>3794</sup> In contrast, Takaku states merely  
8 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary  
9 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study  
10 was attributable to fish oil in general, not EPA specifically.

11 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate  
12 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other  
13 studies cited by Defendants suggest that EPA increases LDL-C.<sup>3795</sup> Defendants identify no other  
14 basis upon which a person of ordinary skill would have sought to combine the Omacor  
15 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

16 (ii) Nozaki and/or Hayashi  
17 Would Not Have Rendered  
18 the Asserted Claims Obvious

18 Defendants contend that the asserted claims of the ’920 patent would have been obvious  
19 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
20 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

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22 <sup>3792</sup> Takaku at Fig. 14, ICOSAPENT\_DFNDT00006883.

23 <sup>3793</sup> Takaku at ICOSAPENT\_DFNDT00006897.

24 <sup>3794</sup> Takaku at ICOSAPENT\_DFNDT00006897.

<sup>3795</sup> See, e.g., Rambjor.

1 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
2 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
3 very high TG patient population.

4 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
5 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
6 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
7 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
8 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
9 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
10 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
11 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
12 patient population were abnormally high and would not have relied upon these results. Further,  
13 the person of skill in the art would not have looked to this patient population to predict the Apo-  
14 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
15 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
16 levels.<sup>3796</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
17 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
18 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
19 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
20 to the very high TG patient population.

21 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
22 the EPA and the DHA content in the composition that was administered is unknown. A person  
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24 <sup>3796</sup> Nozaki at 256.

1 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
2 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
3 C were not statistically significant.<sup>3797</sup> Further, the person of skill in the art would not have  
4 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
5 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
6 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
7 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
8 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
9 administered to the very high TG patient population.

10 Further, Hayashi was a small study conducted in only Japanese patients and was not  
11 placebo controlled. This study would not have been extrapolated to Western populations  
12 because the Japanese diet contains much more fish and has a number of other different attributes.  
13 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
14 populations. In fact, Defendants' own reference states that the results from studies where the  
15 patient population is exclusively Japanese cannot be generalized to other populations.<sup>3798</sup> The  
16 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
17 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
18 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
19 the Japanese respond differently to lipid lowering agents than Westerners.

20 Further, Defendants have failed to offer a purported combination of references as part of  
21 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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23 <sup>3797</sup> Hayashi at 26, Table I.

24 <sup>3798</sup> Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 motivation to combine Nozaki and Hayashi with the other references of their purported  
2 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
3 references.

4 (iii) Grimsgaard, Mori 2000  
5 and/or Maki Do Not Disclose  
6 Purported Knowledge that  
7 DHA was Responsible for the  
8 Increase in LDL-C

9 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
10 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
11 C levels.”<sup>3799</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
12 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
13 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”  
14 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
15 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.  
16 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
17 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or  
18 Maki—as in very-high TG patients because patients with higher TG levels had different lipid  
19 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
20 considered fundamentally different from patients with borderline-high or high triglycerides from  
21 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of  
22 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

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<sup>3799</sup> Defendants’ Joint Invalidity Contentions at 398.



1 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would  
2 substantially increase LDL-C in patients with very high TG levels.

3 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known  
4 that “DHA was responsible for the increase in LDL-C levels.”<sup>3800</sup> The discussion related to  
5 Grimsgaard in Section V.H.3.c.1.a.ii.a.i and Mori 2000 in Section V.H.3.c.1.a.i.a.iii is  
6 incorporated herein by reference.

7 Defendants argue that Maki discloses the administration of purified DHA resulted in the  
8 desired reduction of TGs, but also significantly increased LDL-C levels.<sup>3801</sup> Maki was designed  
9 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with  
10 below-average levels of HDL-C levels.<sup>3802</sup> The DHA supplemented group was administered  
11 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,  
12 monounsaturated and polyunsaturated fatty acids.<sup>3803</sup> Therefore, Maki demonstrated that when  
13 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average  
14 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is  
15 observed.<sup>3804</sup> However, one cannot attribute the rise in LDL-C solely to DHA, because the  
16 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have  
17 also contributed to the elevation in LDL cholesterol.”<sup>3805</sup> Further, Maki admits that the  
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<sup>3800</sup> Defendants’ Joint Invalidity Contentions at 395.

20 <sup>3801</sup> Defendants’ Joint Invalidity Contentions at 398.

21 <sup>3802</sup> Maki at 190.

22 <sup>3803</sup> Maki at 191.

23 <sup>3804</sup> Maki at 195.

24 <sup>3805</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

1 “mechanism(s) responsible for the changes in the lipid profile associated with DHA  
2 supplementation are not fully understood.”<sup>3806</sup> Therefore, the results of Maki are inconclusive as  
3 to DHA’s effect alone on LDL-C levels.

4 Defendants mischaracterize the rise in LDL-C associated with the administration of  
5 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-  
6 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in  
7 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol  
8 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of  
9 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level  
10 less worrisome.”<sup>3807</sup> Therefore, when one of ordinary skill in the art reviewed all the lipid effects  
11 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was  
12 “less worrisome” because of the “potentially favorable effects on triglycerides, the  
13 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense  
14 particles.”<sup>3808</sup>

15 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
16 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
17 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
18 has little effect on LDL-C levels.<sup>3809</sup> Defendants identify no other basis upon which a person of  
19 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,  
20 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

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22 <sup>3806</sup> Maki at 197.

23 <sup>3807</sup> Maki at 197.

24 <sup>3808</sup> Maki at 197.

<sup>3809</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 (iii) The '920 Patent is not Obvious Over the  
2 Omacor PDR/Lovaza PDR, in Combination  
3 with Katayama in View of Satoh and/or in  
4 View of Satoh or Shinozaki in Further View  
5 of Contacos

6 With respect to the '920 patent, Defendants present a combination of five references: “the  
7 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering  
8 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in  
9 further view of Contacos.”<sup>3810</sup> Defendants also present charts purporting to assert that an  
10 additional 60 references may be combined in order to render the Claims obvious. Not only do  
11 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate  
12 references, they additionally do not suggest any identify for combining these references.  
13 Although Defendants need not point to an explicit statement in the prior art motivating the  
14 combination of these references, any assertion of an “apparent reason” to combine must find a  
15 basis in the factual record.<sup>3811</sup> Defendants’ unsupported cobbling of selective disclosures  
16 represents hindsight reconstruction.<sup>3812</sup> Defendants’ contentions are no more than an assertion

17 <sup>3810</sup> Defendants’ Joint Invalidity Contentions at 395.

18 <sup>3811</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
19 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
20 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
21 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi  
22 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
23 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
24 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3812</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that certain claim elements were known in the prior art. Throughout their contentions,  
2 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
3 even the reference as a whole. Each reference, however, must be evaluated for all that it  
4 teaches.<sup>3813</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
5 obviousness.

6 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
7 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty  
8 acid compositions or administration period. The Lovaza PDR further does not disclose a method  
9 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza  
10 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference  
11 would cause a significant increase in LDL-C levels in the very high TG patient population, for  
12 whom the product is indicated. At most, the Lovaza PDR discloses administration of a  
13 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an  
14 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG  
15 levels.

16 Defendants formulate an obviousness argument that relies on Contacos.<sup>3814</sup> However,  
17 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim  
18 element or an “apparent reason” or motivation to combine the elements in the manner  
19 claimed,<sup>3815</sup>.

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21 <sup>3813</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 <sup>3814</sup> *Id.*

23 <sup>3815</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
24 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v. Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and  
2 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,  
3 Contacos fails to provide motivation to administer purified EPA to a very high TG patient  
4 population. Contacos also fails to provide motivation to administer purified EPA to a very high  
5 TG patient population.

6 The proposed combinations do not render the independent claims of the '920 patent  
7 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
8 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally  
9 and the Lovaza package insert specifically) during prosecution.<sup>3816</sup>

10 The analysis of the independent claims of the '920 patent is incorporated into all asserted  
11 claims that depend from those Claims.

12 (a) A Person of Ordinary Skill Would  
13 Not Have Been Motivated to  
14 Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with EPA of  
the Recited Composition

15 For an invention to be obvious, there must have been an "apparent reason" to make it.  
16 The subject matter of the '920 patent claims would not have been obvious in light of these  
17 references because a person of ordinary skill would not have been motivated to purify EPA or  
18 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
19 levels without an increase in LDL-C levels.

20 (i) Katayama, Satoh and/or  
21 Shinozaki Do Not Disclose  
Purported Known Clinical

22 \_\_\_\_\_  
23 <sup>3816</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play").

1  
2  
3 Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the “known clinical  
4 benefits of administering pure EPA - lowering triglycerides without raising LDL-C.” As  
5 discussed in Section V.H.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely  
6 confirms the safety of long term treatment of Epadel and its ability to lower both serum total  
7 cholesterol and triglyceride levels. Katayama does not mention LDL-C levels at all, let alone  
8 discuss any purported “benefits” observed related to LDL-C. Katayama does not disclose or  
9 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary  
10 skill view these references as teaching such a benefit for very-high TG patients.

11 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
12 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
13 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when  
14 compared to baseline, there was no significant effect when compared to placebo.<sup>3817</sup>

15 Defendants’ characterization of Satoh as disclosing the lowering of TG levels without increasing  
16 LDL-C to be a “clinical benefit” is incorrect.<sup>3818</sup> Satoh does not disclose or suggest that the  
17 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these  
18 references as teaching such a benefit for very-high TG patients. As discussed above, one of  
19 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500  
20 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,  
21 however, would have expected that fish oils (and other TG lowering agents) would substantially

22  
23 <sup>3817</sup> Satoh at 145.

24 <sup>3818</sup> Defendants’ Joint Invalidation Contentions at 395 and 396.

1 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to  
2 administer purified EPA to a very high TG patient population.

3 Further, Satoh was a small study conducted in only Japanese patients. This study would  
4 not have been extrapolated to Western populations because the Japanese diet contains much  
5 more fish and has a number of other different attributes. The Japanese consume a higher amount  
6 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference  
7 states that the results from studies where the patient population is exclusively Japanese cannot be  
8 generalized to other populations.<sup>3819</sup> The Japanese diet comprises between 8 and 15 times more  
9 EPA and DHA than typical the typical Western diet. The Western diet typically consists of  
10 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a  
11 person of ordinary skill would understand that the Japanese respond differently to lipid lowering  
12 agents than Westerners.

13 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))  
14 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.  
15 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without  
16 increasing LDL-C to be a "clinical benefit" is incorrect.<sup>3820</sup> Shinozaki says nothing about an  
17 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by  
18 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."<sup>3821</sup> In  
19 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis  
20  
21

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22 <sup>3819</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

23 <sup>3820</sup> Defendants' Joint Invalidation Contentions at 395 and 396.

24 <sup>3821</sup> Shinozaki at 107-109.

1 upon which a person of ordinary skill would have sought to combine the composition disclosed  
2 in Shinozaki.

3 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion  
4 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by  
5 Defendants suggest that EPA increases LDL-C.<sup>3822</sup> Defendants identify no other basis upon  
6 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,  
7 Satoh, Shinozaki and/or Contacos.

8 (ii) Geppert and/or Kelley Do  
9 Not Disclose Purported  
10 Knowledge that DHA was  
11 Responsible for the Increase  
12 in LDL-C

11 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
12 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
13 C levels.”<sup>3823</sup> Defendants' caveat of DHA being “alone or in a mixture” is telling that it was *not*  
14 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
15 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”  
16 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the  
17 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,  
18 respectively. As discussed above in Section III, a person of ordinary skill would not expect the  
19 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or  
20 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid  
21 responses compared to patients with lower TG levels. Patients with very-high TG levels were  
22

23 <sup>3822</sup> See, e.g., Rambjor.

24 <sup>3823</sup> Defendants' Joint Invalidity Contentions at 398.



1 considered fundamentally different from patients with borderline-high or high triglycerides from  
2 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a  
3 person of ordinary skill in the art would have expected that fish oils (and other TG lowering  
4 agents) would not increase LDL-C substantially in patients with normal to borderline high TG  
5 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in  
6 patients with very high TG levels.

7 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA  
8 was responsible for the increase in LDL-C levels.”<sup>3824</sup> Both Geppert and Kelley administer  
9 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.  
10 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the  
11 independent effects of DHA because it is not clear how much of the supplement’s effects can be  
12 attributed to DHA.<sup>3825</sup> For example, Defendants’ own prior art teaches that changes in fatty acid  
13 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.<sup>3826</sup>

14 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to  
15 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been  
16 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior  
17 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”<sup>3827</sup> Rather than reading  
18 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior  
19 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there  
20 was confusion in the art and it was unclear whether DHA increased LDL-C.

21  
22 <sup>3824</sup> Defendants’ Joint Invalidation Contentions at 396.

23 <sup>3825</sup> See Mori 2006 at 96.

24 <sup>3826</sup> Maki at 197.

<sup>3827</sup> Geppert at 784.

1 A person of ordinary skill would have expected that Geppert's results would be  
2 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA  
3 was the only component of fish oil to increase LDL-C. For example, there is no data comparing  
4 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying  
5 explain the mechanism of LDL-C increase.<sup>3828</sup> A person of ordinary skill would have not  
6 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

7 Defendants contend that Kelley shows that DHA was responsible for the increase in  
8 LDL-C.<sup>3829</sup> In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day  
9 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible  
10 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon  
11 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate  
12 therapy.<sup>3830</sup> Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in  
13 context with the other lipid effects reported in the study. Kelley states that:

14 DHA supplementation may lower the risk of CVD by reducing  
15 plasma triacylglycerols; triacylglycerol:HDL; the number of small,  
16 dense LDL particles; and mean diameter of VLDL particles. An  
17 increase was observed in fasting LDL cholesterol, but it is unlikely  
18 this increase is detrimental because no increase was observed in the  
19 overall number of LDL particles; actually, there was an 11%  
20 reduction that was statistically not significant. The reason LDL  
21 cholesterol increased despite no change in LDL particle number was  
22 that the LDL particles were made larger and hence more cholesterol  
23 rich by DHA treatment.<sup>3831</sup>

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22 <sup>3828</sup> *Id.*

23 <sup>3829</sup> Defendants' Joint Invalidation Contentions at 396.

24 <sup>3830</sup> Kelley at 329.

<sup>3831</sup> Kelley at 329

1 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation  
2 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle  
3 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the  
4 concentrations of atherogenic lipids and lipoproteins and increased concentrations of  
5 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular  
6 health.”<sup>3832</sup> Rather than concluding that DHA was uniquely responsible for a rise in LDL-C  
7 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely  
8 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with  
9 negative attributes, a person of ordinary skill would understand that the reference taught towards  
10 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400  
11 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the  
12 very high TG patient population to be different in terms of their response to lipid therapy,  
13 including administration of DHA. A person of ordinary skill in the art would have expected that  
14 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with  
15 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a  
16 substantial increase in LDL-C in patients with very high TG levels.

17 Therefore, Geppert and/or Kelley fail to substantiate Defendants’ assertion that it was  
18 known that DHA was responsible for the increase in LDL-C levels.

19 Throughout their contentions, Defendants’ selectively cite to data points in a reference  
20 without considering other disclosures or even the reference as a whole. Each reference,  
21 however, must be evaluated for all that it teaches.<sup>3833</sup> As is the case with Kelley, Defendants use

22 \_\_\_\_\_  
23 <sup>3832</sup> Kelley at 324, 332.

24 <sup>3833</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 hindsight to characterize a reference based on LDL-C levels alone without considering the other  
2 lipid effects studied, considered and reported.<sup>3834</sup> The isolated manner in which Defendants  
3 select such data points is not the approach that a person of ordinary skill would have taken at the  
4 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.  
5 A person of ordinary skill would take into consideration the entire disclosure of a reference,  
6 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,  
7 without explanation, the other effects of DHA that a person of ordinary skill would consider.  
8 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a  
9 favorable effect in hypertriglyceridemic patients.

10 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was  
11 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,  
12 without explanation, other studies that demonstrate that DHA decreases or has little effect on  
13 LDL-C levels.<sup>3835</sup> Defendants identify no other basis upon which a person of ordinary skill  
14 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,  
15 Geppert and/or Kelley.

16 (iv) A Person of Ordinary Skill Would Not Have  
17 Been Motivated to Find an Omega-3 Fatty  
18 Acid "therapy that would reduce TG levels  
19 in patients with TG levels  $\geq 500$  mg/dL  
20 without negatively impacting LDL-C  
21 levels."

22 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG  
23 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there  
24

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22 <sup>3834</sup> Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation  
23 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean  
24 diameters of these particles in fasting and postprandial plasma.").

<sup>3835</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect  
2 a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time  
3 of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused  
4 by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering  
5 mechanism. The therapies that were available at the time of the invention to treat very-high TGs  
6 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin  
7 was associated with a highly undesirable side effects—including “flushing” (or reddening of the  
8 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.<sup>3836</sup>  
9 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in  
10 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed  
11 fibrates in combination with an LDL-C lowering medication such as a statin.<sup>3837</sup> However, the  
12 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.<sup>3838</sup>  
13 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a  
14 combination fibrate/statin course of treatment.<sup>3839</sup> Finally, Lovaza/Omacor were also effective at  
15 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels  
16 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins  
17 in order to mitigate increased LDL-C.

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20 <sup>3836</sup> See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher  
21 doses of niacin due to side effects).

22 <sup>3837</sup> Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate  
is often required to achieve LDL-C and non-HDL-C goals”);

23 <sup>3838</sup> See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with  
statins.”).

24 <sup>3839</sup> See *Id.*, ¶ 17

1 In any event, a person of ordinary skill in the art would have understood that omega 3-  
 2 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high  
 3 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would  
 4 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs  
 5 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3840</sup>	-20%	+45%
Lovaza/Omacor <sup>3841</sup>	-6%	+45%

9  
 10 That Epadel has been approved for decades but not approved for use in the very high TG  
 11 patient population prior to the invention of the asserted patents is a real-world reflection of the  
 12 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
 13 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
 14 been countless studies conducted which administer Epadel and report the effects observed.  
 15 Although a few studies administer Epadel to a patient population which included a few patients  
 16 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
 17 administration of Epadel to patients with very-high TG levels, reflecting the lack of motivation.

18 Defendants offer no “apparent reason” to administer EPA as claimed to patients with  
 19 fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on  
 20 Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients  
 21  
 22

23 <sup>3840</sup> Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

24 <sup>3841</sup> Chan 2002 I at 2381 (Table 3).

1 with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”<sup>3842</sup>

2 Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500  
3 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG  
4 reduction and the increased conversion of VLDL to LDL particles.<sup>3843</sup>

5 It was well known at the time of the invention that omega-3 fatty acids, including both  
6 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant  
7 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3  
8 fatty acids worked in part by inhibiting VLDL production and improving the conversion of  
9 VLDL particles to LDL.<sup>3844</sup> A person of ordinary skill in the art understood that EPA and DHA  
10 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when  
11 discussing the TG-lowering mechanism of omega-3 fatty acids.<sup>3845</sup> The discussion related to the  
12 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and  
13 incorporated herein by reference.

14 In fact, it was well understood that the degree of LDL-C elevation observed with  
15 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG  
16 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels  
17  
18

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19 <sup>3842</sup> Defendants’ Joint Invalidity Contentions at 397.

20 <sup>3843</sup> See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese  
21 results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and  
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in  
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

22 <sup>3844</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”)

23 <sup>3845</sup> Bays I, at 398; Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in *The*  
Johns Hopkins Textbook of Dyslipidemia 245, 247 (Peter O. Kwiterovich Jr. ed., 2009 (Bays III))

1 the most in patients with the highest pretreatment TG levels.<sup>3846</sup> Therefore, a person of ordinary  
2 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct  
3 consequence of lowering triglycerides in patients with TG levels  $\geq 500$  mg/dL. The rise in LDL-  
4 C was often offset by concurrent treatment with statins.<sup>3847</sup> The safety and efficacy of using  
5 prescription omega-3 in combination with a statin has been well-established.<sup>3848</sup>

6 Although an increase in LDL-C was generally observed when omega-3 fatty acids were  
7 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a  
8 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.  
9 Therefore, the final LDL-C concentration may still be in the normal range.<sup>3849</sup> Furthermore, it  
10 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.<sup>3850</sup>

11 In two pivotal studies in very-high TG patients, both of which used prospective,  
12 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL  
13 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).<sup>3851</sup> Correspondingly, prescription  
14

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15 <sup>3846</sup> See Bays 2008 Rx Omega-3 p. 402.

16 <sup>3847</sup> See Harris 2008 at 14, McKenney at 722.

17 <sup>3848</sup> McKenney at 722-23.

18 <sup>3849</sup> See Westphal at 918, Harris 1997 at 389.

19 <sup>3850</sup> See Pownall at 295 (stating that “[t]reatment with  $\omega$ -3 fatty acids appear to change the lipid profile of individuals  
20 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesteryl ester  
21 transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he  
22 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-  
23 high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the  
24 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute  
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this  
rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty  
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in  
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by  
decreased non-HDL-C levels (TC minus HDL-C”).

<sup>3851</sup> McKenney 2007 at 721 (citing Harris 1997 and Pownall).



1 | omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.<sup>3852</sup> Therefore,  
2 | “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can  
3 | substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net  
4 | effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in  
5 | patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also  
6 | known to alter lipoprotein particle size and composition in a favorable manner by decreasing the  
7 | number of small, dense LDL particles to larger LDL particles.<sup>3853</sup> Lovaza/Omacor “adversely  
8 | raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration  
9 | reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”<sup>3854</sup>  
10 | Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3  
11 | fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not  
12 | only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention  
13 | of [coronary heart disease].”<sup>3855</sup>

14 |         Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at  
15 | the time of the claimed inventions would have been motivated to find a therapy that would  
16 | reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting  
17 | LDL-C levels,”<sup>3856</sup> one of ordinary skill in the art at the time of the invention understood that the  
18 | rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with  
19 | very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to  
20 |

21 | \_\_\_\_\_  
22 | <sup>3852</sup> McKenney 2007 at 722 (*see* Fig. 1).

23 | <sup>3853</sup> McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

24 | <sup>3854</sup> Stalenhoef at 134.

<sup>3855</sup> Harris 1997 at 389.

<sup>3856</sup> Defendants’ Joint Invalidity Contentions at 397.

1 increase in very-high TG patients, and in some instances the rise was not concerning because  
2 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final  
3 concentration would still be in the normal range. When LDL-C levels increased beyond what  
4 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively  
5 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of  
6 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to  
7 identify any other basis upon which a person of ordinary skill would have been motivated to find  
8 a therapy that would reduce TG levels in patients with very-high TG levels without negatively  
9 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood  
10 that EPA therapy would *not* reduce Apo-B<sup>3857</sup> (which is a reflection of total atherogenic  
11 lipoproteins)<sup>3858</sup> in very high TG patients, and accordingly would not have been motivated to  
12 administer the claimed EPA composition to the very high TG patient population.

13 Defendants make the conclusory allegation that “routine optimization” by a person of  
14 ordinary skill would yield the claimed invention.<sup>3859</sup> Defendants, however, have offered no  
15 explanation to support that allegation and they further fail to establish any of the required criteria  
16 of “routine optimization” or the prerequisites to this argument. They also fail to provide any  
17 factual detail to support their allegation and they fail to link the allegation to any particular claim  
18 or claim element. Defendants mere allegation constitute an improper placeholder to later  
19 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,  
20 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the

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22 <sup>3857</sup> *see* Section V.O.

23 <sup>3858</sup> *see* Section III.

24 <sup>3859</sup> *See, e.g.*, Defendants’ Joint Invalidation Contentions at 392.

1 combinations alleged by Defendants and, for the same reasons, it would not be routine to  
2 combine such references. Where, for example, defendants argue that it would be routine to go  
3 from the high TG patient population to the very high TG patient population,<sup>3860</sup> they provide no  
4 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill  
5 would have understood these patient populations to be distinct with different impacts of lipid  
6 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would  
7 not have considered the dosage modification suggested by defendants to be routine; Defendants'  
8 argument to the contrary represents hindsight bias.

9 In addition, a person of ordinary skill would have no motivation to combine these  
10 references because EPA would have been expected to have same result as the mixture of EPA  
11 and DHA used in Lovaza/Omacor.

12 (b) Defendants Have Not Shown It Would Have Been  
13 Obvious to Administer Purified EPA in the Dosing  
14 Regimen Recited in the Claims

14 (i) The '920 Patent is not Obvious Over WO  
15 '118 or WO '900, in Combination with the  
16 Lovaza PDR, and Further in View of Leigh-  
17 Firbank and/or Mori 2000

16 With respect to the '920 patent, Defendants present a combination of five references:  
17 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the  
18 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."<sup>3861</sup> Defendants also  
19 present charts arguing that an additional 61 references may be combined in order to render the  
20 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill  
21

22 \_\_\_\_\_  
23 <sup>3860</sup>Defendants' Joint Invalidation Contentions at 399-400.

24 <sup>3861</sup>Defendants' Joint Invalidation Contentions at 402.

1 would combine 61 separate references, they additionally do not identify any motivation for  
2 combining these references.<sup>3862, 3863</sup> Although Defendants need not point to an explicit statement  
3 in the prior art motivating the combination of these references, any assertion of an “apparent  
4 reason” to combine must find a basis in the factual record.<sup>3864</sup> Defendants’ unsupported cobbling  
5 of selective disclosures represents hindsight reconstruction.<sup>3865</sup> Defendants’ contentions are no  
6 more than an assertion that certain claim elements were known in the prior art. Throughout their  
7 contentions, Defendants’ selectively cite to data points in a reference without considering other  
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10 <sup>3862</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of the references cited in  
11 Sections II and V.A and B, including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi,  
12 Katayama, Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh,  
13 Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert,  
Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a  
person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to  
meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine  
these references. *See* Defendants’ Joint Invalidity Contentions at 401.

14 <sup>3863</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
15 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
16 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person  
having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 392-93.

17 <sup>3864</sup> *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
19 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point  
“must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation  
20 to select and then modify a lead compound to arrive at the claimed invention,” which turns on the known “properties  
and limitations of the prior art compounds”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F.  
21 Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima*  
*facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and  
22 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art  
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>3865</sup> *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
2 that it teaches.<sup>3866</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
3 obviousness.

4 WO '118 is directed at the composition containing EPA for the purpose of preventing the  
5 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118  
6 is directed, "in particular, [to] preventing occurrence of cardiovascular events in  
7 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the  
8 risk of the cardiovascular events."<sup>3867</sup> Contrary to Defendants' assertion that WO '118 discloses  
9 "the administration of 4 g of pure EPA with no DHA,"<sup>3868</sup> WO '118 fails to disclose the claimed  
10 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive  
11 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified  
12 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction  
13 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of  
14 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in  
15 the disclosed composition.<sup>3869</sup>

16 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target  
17 population of the claimed invention. The asserted claims are directed to persons with severe  
18 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only  
19 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.<sup>3870</sup> WO

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20 <sup>3866</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>3867</sup> WO '118 at 9.

22 <sup>3868</sup> Defendants' Joint Invalidation Contentions at 402.

23 <sup>3869</sup> WO '118 at 22-23.

24 <sup>3870</sup> WO '118 at 8.

1 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to  
2 patients with borderline-high to high TG levels, since the primary goal for patients with very-  
3 high TG is to prevent acute pancreatitis by decreasing TG levels.<sup>3871</sup>

4 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the  
5 effectiveness of the substances for treating hypertriglyceridemia.<sup>3872</sup> WO '118 states that  
6 "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-  
7 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +  
8 DHA-E) are not particularly limited as long as intended effects of the present invention are  
9 attained."<sup>3873</sup> It further states that "the composition is preferably the one having a high purity of  
10 EPA-E and DHA-E."<sup>3874</sup> Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C,  
11 Apo-B, or Lp-PLA2.

12 WO '900 is directed to a process for producing purified EPA from a culture of micro-  
13 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels  
14 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed  
15 pharmaceutical composition with the specified dosage or administration period, or the claimed  
16 method to effect the specified TG reduction without substantially increasing LDL-C. WO '900  
17 only discloses the method of producing purified EPA for therapeutic use, it does not teach  
18 *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient  
19 population or method of treatment.

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21 <sup>3871</sup> See Section III.

22 <sup>3872</sup> WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

23 <sup>3873</sup> WO '118 at 22-23.

24 <sup>3874</sup> WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists  
2 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of  
3 them.<sup>3875</sup> Moreover, WO '900 does not teach the desired effect of EPA other than commenting  
4 generally that it “may promote health and ameliorate or even reverse the effects of a range of  
5 common diseases.”<sup>3876</sup> It has no discussion, for example, on any TG-lowering effect of EPA.  
6 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*  
7 undesired effect of DHA or other impurities it is trying to prevent other than commenting  
8 generally that “the desired effects of EPA may be limited or reversed” by them.<sup>3877</sup> It has no  
9 discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claims of the '920 patent  
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO  
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package  
13 insert specifically) during prosecution.<sup>3878</sup>

14 The analysis of the independent claims of the '920 patent is incorporated into all asserted  
15 claims that depend from those Claims.

16 (a) Leigh-Firbank and Mori 2000 Do  
17 Not Disclose Purported Knowledge  
18  
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20 <sup>3875</sup> See, e.g., '900 Pub. at 16-17.

21 <sup>3876</sup> '900 Pub. at 5.

22 <sup>3877</sup> '900 Pub. at 39.

23 <sup>3878</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 that DHA was Responsible for the  
2 Increase in LDL-C

3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known  
5 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-  
6 C levels as evidenced by Leigh-Firbank or Mori 2000.”<sup>3879</sup>

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with  
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need  
9 not point to an explicit statement in the prior art motivating the combination of these references,  
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>3880</sup>  
11 Defendants’ unsupported cobbling of selective disclosures represents hindsight  
12 reconstruction.<sup>3881</sup> Defendants’ contentions are no more than an assertion that certain claim  
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to  
14 establish *prima facie* obviousness.

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16 <sup>3879</sup> Defendants’ Joint Invalidity Contentions at 402.

17 <sup>3880</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
*Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 <sup>3881</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).



1 Contrary to Defendants’ assertion, Leigh-Firbank and Mori 2000 do *not* disclose that  
2 DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank  
3 and Mori 2000 in Section V.H.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank  
4 cannot comment on the effect of EPA and DHA alone because it did not administer EPA and  
5 DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does  
6 not offer any disclosure regarding the effect of EPA and DHA separately or gain any  
7 understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000  
8 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is  
9 preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation  
10 to combine with WO ‘118 or WO ‘900. Engaging in hindsight bias, Defendants ignore, without  
11 explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants  
12 fail to identify any other basis upon which a person of ordinary skill would have sought to  
13 combine Mori 2000 with the Lovaza PDR.

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants  
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little  
17 effect on LDL-C levels.<sup>3882</sup> Defendants identify no other basis upon which a person of ordinary  
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or  
19 Mori.

- 20 (ii) The ‘920 patent is not Obvious Over WO  
21 ‘118, WO ‘900, Grimsgaard, Mori 2000  
22 and/or Maki in Combination with the  
23 Omacor PDR/Lovaza PDR, and Further in

24 <sup>3882</sup> See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '920 patent, Defendants present a combination of nine references:

“WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku.”<sup>3883</sup> Defendants also present charts arguing that an additional 56 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 56 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>3884</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>3885</sup> Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

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<sup>3883</sup> Defendants’ Joint Invalidity Contentions at 402.

<sup>3884</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3885</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or  
2 even the reference as a whole. Each reference, however, must be evaluated for all that it  
3 teaches.<sup>3886</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
4 obviousness.

5 The discussion related to WO ‘118 and WO ‘900 in Section V.H.3.c.1.b.i is incorporated  
6 herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section  
7 V.H.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that “Grimsgaard and  
8 Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA.”  
9 However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the  
10 *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to  
11 administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other  
12 basis upon which a person of ordinary skill would have sought to combine the composition  
13 disclosed in Grimsgaard or Mori 2000.

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art  
15 to use EPA as described in WO ’118, WO ‘900, Grimsgaard or Mori 2000 in the treatment  
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their  
17 assertions fail to provide a motivation for combining the references.<sup>3887</sup> Although Defendants  
18 need not point to an explicit statement in the prior art motivating the combination of these  
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual  
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21

22 \_\_\_\_\_  
23 <sup>3886</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>3887</sup> Defendants’ Joint Invalidity Contentions at 402.

1 record.<sup>3888</sup> Defendants’ assertions related to motivation are insufficient,<sup>3889</sup> and accordingly  
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or  
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference  
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the  
6 manner claimed.<sup>3890</sup> Therefore, Defendants should be precluded from relying on this these  
7 references.

8 As discussed above in Section V.H.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only  
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both  
10 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer  
11 purified EPA to the very high TG patient population. As discussed above in Section

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13 <sup>3888</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
14 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
15 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
16 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*  
17 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
18 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
19 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and  
20 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
21 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
22 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
23 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
24 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>3889</sup> For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating  
hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any  
basis for that statement. While the paragraph associated with that statement makes assertions regarding the  
disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO  
’118. See Defendants’ Joint Invalidity Contentions at 403.

<sup>3890</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
*Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 V.H.3.c.1.a.ii.a.i, Takaku candidly acknowledges that “only a few subjects were examined” and  
2 cautions against drawing a conclusion “only from the results of the present study.”<sup>3891</sup> Further,  
3 the study did not include any placebo control, therefore, a person of ordinary skill in the art  
4 would understand these reports do not provide the ability to conclude that the observed lipid  
5 effects would have occurred independent of the drug that is administered. In addition, the study  
6 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have  
7 expected the results to be applicable to the general population.<sup>3892</sup>

8 The proposed combination does not render the independent claims of the ’920 patent  
9 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
10 considered WO ’118, WO ’900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and  
11 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.<sup>3893</sup>

12 The analysis of the independent claims of the ’920 patent is incorporated into all asserted  
13 claims that depend from those Claims.

- 14 (a) Grimsgaard, Mori 2000 and/or Maki  
15 Do Not Disclose Purported  
16 Knowledge that DHA was  
17 Responsible for the Increase in LDL-  
18 C

17 Defendants contend that a “person of ordinary skill in the art would have been motivated  
18 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known  
19

20 <sup>3891</sup> Takaku at ICOSAPENT\_DFNDT00006897.

21 <sup>3892</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.”)

22 <sup>3893</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the  
23 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
24 and convincing standard came into play”).

1 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is  
2 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or  
3 Maki.”<sup>3894</sup>

4 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose  
5 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,  
6 Mori 2000 and/or Maki in Section V.H.3.c.1.a.ii.a.iii is incorporated herein by reference. A  
7 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA  
8 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,  
9 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although  
10 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not  
11 disclose administration of DHA to the requisite patient population and teaches that DHA is  
12 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,  
13 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
14 would consider. Most controlled studies in patients with normal to high baseline TG levels  
15 indicated that DHA had little or no effect on LDL-C.<sup>3895</sup> Therefore, a person of ordinary skill  
16 would not have concluded that DHA increases LDL-C in patients with normal to high baseline  
17 TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is  
18 administered to patients with below-average levels of HDL-C levels and borderline-high TG  
19 levels, a significant increase in LDL-C is observed.<sup>3896</sup> However, one of ordinary skill in the art  
20

21 \_\_\_\_\_  
<sup>3894</sup> Defendants’ Joint Invalidity Contentions at 403.

22 <sup>3895</sup> Mori 2000 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
23 controlled, found an increase in LDL-C after DHA administration.

24 <sup>3896</sup> Maki at 195.

1 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.<sup>3897</sup>  
2 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

3 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion  
4 that it was known that DHA was responsible for the increase in LDL-C levels. Further,  
5 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
6 has little effect on LDL-C levels.<sup>3898</sup> Defendants identify no other basis upon which a person of  
7 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,  
8 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

9 (iii) A Person of Ordinary Skill Would Not Have  
10 Been Motivated to Administer Purified EPA  
11 in the Treatment Regimen Recited in the  
12 Claims

12 For an invention to be obvious, there must have been an “apparent reason” to make it.  
13 Defendants assert that a “person of ordinary skill in the art would have been motivated to  
14 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to  
15 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”<sup>3899</sup> However, as  
16 set forth below, Defendants fail to address why a person of ordinary skill in the art would have  
17 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides  
18 greater than or equal to 500 mg/dL.

19 A person of ordinary skill in the art would have understood that omega 3-fatty acids,  
20 including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients,

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21 <sup>3897</sup> Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*  
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A  
number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated  
fat and cholesterol, both of which are known to elevate LDL-C.”).

23 <sup>3898</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 <sup>3899</sup> Defendants’ Joint Invalidity Contentions at 215.

1 as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been  
2 motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing  
3 LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate <sup>3900</sup>	-20%	+45%
Lovaza/Omacor <sup>3901</sup>	-6%	+45%

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8 That Epadel has been approved for decades but not approved for use in the very high TG  
9 patient population prior to the invention of the asserted patents is a real-world reflection of the  
10 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.  
11 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have  
12 been countless studies conducted which administer Epadel and report the effects observed.  
13 Although a few studies administer Epadel to a patient population which included a few patients  
14 with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the  
15 administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

16 Defendants further argue that the disclosure in WO '118 would combine with the prior art  
17 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to  
18 increase LDL-C levels while products containing only EPA did not," and second, "WO '118  
19 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-  
20 purified ethyl-EPA."<sup>3902</sup> Both of the "reasons" identified by Defendants are false.

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22 <sup>3900</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

23 <sup>3901</sup> Chan 2002 I at 2381 (Table 3).

24 <sup>3902</sup> Defendants' Joint Invalidity Contentions at 404.



1           Regarding Defendants’ first reason, that “products containing DHA were reported to  
2 increase LDL-C levels while products containing only EPA did not,” most controlled studies in  
3 patients with normal to high baseline TG levels indicated that DHA had little or no effect on  
4 LDL-C.<sup>3903</sup> Therefore, a person of ordinary skill would not have concluded that DHA increases  
5 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,  
6 and Theobald do *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,  
7 while EPA does not.” First, Leigh-Firbank cannot comment on the effect of EPA and DHA  
8 alone because it did not administer EPA and DHA separately.<sup>3904</sup> A person of ordinary skill  
9 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect  
10 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA  
11 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with  
12 other saturated and polyunsaturated fatty acids.<sup>3905</sup> Therefore, a person of ordinary skill would  
13 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear  
14 how much of the supplement’s effects can be attributed to DHA.<sup>3906</sup> Kelley does not show that  
15 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a  
16 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase  
17 was induced by fibrate therapy.<sup>3907</sup> Kelley specifically teaches that the increase in LDL-C  
18 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel  
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20 <sup>3903</sup> Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo  
21 controlled, found an increase in LDL-C after DHA administration.

22 <sup>3904</sup> The discussion related to Leigh-Firbank in Section V.H.3.c.1.a.i.a.iii is incorporated herein by reference.

23 <sup>3905</sup> The discussion related to Kelley in Section V.H.3.c.1.a.iii.a.ii is incorporated herein by reference.

24 <sup>3906</sup> See Mori 2006 at 96.

<sup>3907</sup> Kelley at 329.

1 increase in overall LDL particle number. Rather than concluding that DHA was uniquely  
2 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to  
3 disclose that DHA had uniquely beneficial cardioprotective effects.<sup>3908</sup> Finally, Theobald also  
4 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for  
5 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by  
6 7% when compared to placebo. However, the DHA composition that was administered in  
7 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,  
8 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA  
9 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it  
10 impossible to determine whether or how much of the supplement's effects can be attributed to  
11 DHA.<sup>3909</sup> Contrary to Defendants' assertion that there was "a reported advantage to using EPA  
12 vs. DHA in hypertriglyceridemic subjects,"<sup>3910</sup> there was no known advantage to using EPA vs.  
13 DHA. In fact, a number of the references Defendants cite in their contentions ultimately  
14 conclude that DHA supplementation "may represent a more favorable lipid profile than after  
15 EPA supplementation."<sup>3911</sup> In addition, a person of ordinary skill would have recognized any  
16 impact of DHA reported by the study to be applicable to EPA because they would have  
17 understood these substances to function by the same mechanism. Furthermore, as discussed  
18 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in  
19 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients

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21 <sup>3908</sup> Kelley at 324, 332 (Kelley's ultimate conclusion is that "[o]verall, DHA supplementation reduced the  
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins"  
and that "DHA supplementation may improve cardiovascular health.")

23 <sup>3909</sup> See Mori 2006 at 96.

24 <sup>3910</sup> Defendants' Joint Invalidity Contentions at 404.

<sup>3911</sup> Mori 2000 at 1092.

1 because patients with higher TG levels had different lipid responses compared to patients with  
2 lower TG levels.

3           Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in  
4 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”  
5 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been  
6 well documented.<sup>3912</sup> Lovaza/Omacor has been shown to reduce the risk for cardiovascular  
7 death plus nonfatal myocardial infarction and nonfatal stroke.<sup>3913</sup> Omega-3 fatty acids have been  
8 shown to exert cardioprotective effects in both primary and secondary coronary heart disease  
9 prevention trials.<sup>3914</sup> Omega-3 fatty acids were known to reduce TG concentration, have  
10 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure  
11 and/or reduce heart rate.<sup>3915</sup>

12           Defendants argue that a “person of ordinary skill in the art would have appreciated the  
13 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce  
14 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of  
15 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”<sup>3916</sup> As  
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19 <sup>3912</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
20 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA  
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 <sup>3913</sup> See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,  
98 *AM. J. CARDIOL* 71i (2006) (“Bays 2006”).

22 <sup>3914</sup> Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,  
197 *ATHEROSCLEROSIS* 12, 13 (2008) (“Harris 2008”).

23 <sup>3915</sup> Harris 2008 at 13.

24 <sup>3916</sup> Defendants’ Joint Invalidity Contentions at 404-405.

1 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA  
2 and Lovaza/Omacor have been well documented.<sup>3917</sup>

3 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart  
4 disease endpoints as a function of tissue FA composition found that the evidence suggested that  
5 DHA is *more* cardioprotective than EPA.<sup>3918</sup> This study found that “depressed levels of long-  
6 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary  
7 heart disease events.”<sup>3919</sup> Further, the study found that DHA levels, with or without EPA, were  
8 significantly lower in fatal endpoints.<sup>3920</sup> This study suggests that DHA is preferable to EPA—  
9 thus teaching away from the claimed invention.<sup>3921</sup> Defendants rely on hindsight bias to argue  
10 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA  
11 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA  
12 was *more* cardioprotective than EPA.

13 Defendants argue that the following claim elements were known: the administration of  
14 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the  
15 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to

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17 <sup>3917</sup> Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193  
18 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA  
and CHD risk.”) (“Harris 2007”).

19 <sup>3918</sup> Harris 2007 at 8.

20 <sup>3919</sup> *Id.*

21 <sup>3920</sup> Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all  
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 <sup>3921</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of  
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the  
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*  
*Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs.,  
Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the  
prior art ... is strong evidence of nonobviousness.”).

1 patients with high and very high TG levels who were not receiving concurrent lipid altering  
2 therapy, and the dose of 4g/day and 12-week regimen.<sup>3922</sup> Defendants then argue that the “only  
3 question is whether one skilled in the art would have been motivated to use the DHA-free,  
4 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at  
5 least 500 mg/dL as part of the claimed dosage regimen.”<sup>3923</sup>

6 Defendants’ contentions are no more than a recitation that certain claim elements were  
7 known in the prior art. Defendants’ assertions to the contrary represent hindsight  
8 reconstruction.<sup>3924</sup> Notably, Defendants *do not* assert that a person of ordinary skill would have  
9 known that purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL),  
10 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,<sup>3925</sup>  
11 which included a small minority of patients with baseline TG levels  $> 500$  mg/dL to argue that “a  
12 number of prior art references disclosed the administration of purified EPA to patients with TG  
13 levels  $> 500$  mg/dL.”<sup>3926, 3927</sup> The disclosures of Nakamura (one patient), Matsuzawa (disclosure  
14 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the  
15 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of  
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18 <sup>3922</sup> Defendants’ Joint Invalidity Contentions at 405-406.

19 <sup>3923</sup> Defendants’ Joint Invalidity Contentions at 406.

20 <sup>3924</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under  
21 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
22 without any explanation as to how or why the references would be combined to produce the claimed invention.”).

23 <sup>3925</sup> Nakamura, Matsuzawa, and Takaku.

24 <sup>3926</sup> Defendants’ Joint Invalidity Contentions at 405.

<sup>3927</sup> Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels  $> 500$   
mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually  
high and there is no specific disclosure of a single subject with TG levels  $> 500$  mg/dL. Okumuara specifically  
states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

1 ordinary skill in the art would *not* understand these references to relate to the use of EPA in  
2 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions  
3 regarding these references in terms of the very high TG patient population. In Nakamura, one  
4 patient had a baseline TG level > 500 mg/dL.<sup>3928</sup> However, the mean baseline TG for all patients  
5 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was  
6 well below 500 mg/dL.<sup>3929</sup> In Matsuzawa, three patients had TG levels between 400 and 1000  
7 mg/dL and one patient had TG levels > 1,000 mg/dL.<sup>3930</sup> Based on this disclosure, only one  
8 patient definitively had a baseline TG level  $\geq$  500 mg/dL. Further, this one patient was excluded  
9 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol  
10 made it impossible to assess triglyceride levels.”<sup>3931</sup> In Takaku, three patients had baseline TG  
11 levels above 500 mg/dL.<sup>3932</sup> However, the mean baseline TG level for all patients was 245  
12 mg/dL.<sup>3933</sup> Indeed, the mean baseline TG level of the patients in all three studies was well below  
13 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be  
14 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,  
15 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the  
16 Friedewald’s Equation cannot be used for patients with triglyceride levels  $\geq$  400 mg/dL.<sup>3934</sup>  
17 Defendants have failed to identify all of the claimed elements and fail to provide motivation to  
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19 <sup>3928</sup> Nakamura at 23, Table 1.

20 <sup>3929</sup> Nakamura at 23, Tables 1 and 2.

21 <sup>3930</sup> *Id.* at 23.

22 <sup>3931</sup> *Id.* at 10.

23 <sup>3932</sup> Takaku at ICOSAPENT\_DFNDTS00006895.

24 <sup>3933</sup> Takaku at ICOSAPENT\_DFNDTS00006875.

<sup>3934</sup> *See* Matsuzawa at ICOSAPENT\_DFNDTS00006450.

1 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with  
2 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

3 Defendants contend that a “person of ordinary skill in the art would have been motivated  
4 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the  
5 known TG-lowering effects of highly-purified EPA-E.”<sup>3935</sup> This argument is flawed. The prior  
6 art demonstrates a wide range of administration periods utilized in different clinical studies. For  
7 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in  
8 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.  
9 Given the large number of choices of administration periods disclosed in prior art, Defendants  
10 have not shown that a person of ordinary skill would not have been motivated to administer  
11 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

12 Moreover, a person of ordinary skill would not have been motivated to administer highly-  
13 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as  
14 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood  
15 triglycerides.<sup>3936</sup> In fact, Defendants acknowledge in their Joint Invalidation Contentions that  
16 “DHA and EPA were both known to comparably reduce triglycerides, independently of one  
17 another.”<sup>3937</sup> Data from some studies even suggested that DHA or fish oil may reduce  
18 triglyceride more effectively than EPA.<sup>3938</sup> Therefore, a person of ordinary skill would not have  
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<sup>3935</sup> Defendants’ Joint Invalidation Contentions at 406.

21 <sup>3936</sup> Mori 2006 at 98.

22 <sup>3937</sup> Defendants’ Joint Invalidation Contentions at 407.

23 <sup>3938</sup> Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor  
24 (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was  
grater with DHA supplementation than EPA supplementation).

1 | been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination  
2 | of EPA and DHA (such as Lovaza) for 12 weeks.

3 | Defendants argue that a “person of ordinary skill in the art also would have been  
4 | motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant  
5 | reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.<sup>3939</sup> This  
6 | argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with  
7 | *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to  
8 | administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

9 | Defendants also, once again, fail to demonstrate that a person of ordinary skill would have  
10 | chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such  
11 | as Lovaza).

12 | Defendants further argue that “because Katayama and Saito 1998 teach that higher doses  
13 | of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of  
14 | ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a  
15 | dose of 4 g/day rather than a lower dose.”<sup>3940</sup> A person of ordinary skill would not have relied  
16 | on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,  
17 | because these studies were not designed to determine the effect of dose on the degree of TG  
18 | reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower  
19 | dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

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23 | <sup>3939</sup> Defendants’ Joint Invalidation Contentions at 406.

24 | <sup>3940</sup> Defendants’ Joint Invalidation Contentions at 406-07.



1           Moreover, as discussed above, it was well known that both EPA and DHA reduced blood  
2 triglycerides.<sup>3941</sup> Therefore, a person of ordinary skill would not have been motivated to  
3 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of  
4 EPA and DHA (such as Lovaza).

5           Defendants further argue that a “person of ordinary skill in the art would have also been  
6 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with  
7 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much  
8 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito  
9 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”<sup>3942</sup> This argument is  
10 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a  
11 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have  
12 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3  
13 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline  
14 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a  
15 greater decrease in TG levels, in the very high TG patient population, would lead to a greater  
16 increase in LDL-C levels.

17           Defendants contend that a “person of ordinary skill in the art would have been motivated  
18 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a  
19 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to  
20 effect a reduction in TG and LDL-C, if treatment was with statin therapy.” Defendants first  
21 support this argument by asserting that a person of ordinary skill in the art would have known  
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23 <sup>3941</sup> See Section III.

24 <sup>3942</sup> Defendants’ Joint Invalidity Contentions at 407.

1 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is  
2 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA  
3 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,  
4 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in  
5 V.B.4. and 5” to support this proposition, however these references do not disclose or suggest to  
6 a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very  
7 high TG patients.<sup>3943</sup>

8 Defendants next argue again that DHA was known to be responsible for the increase in  
9 LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of  
10 ordinary skill would understand that both EPA and DHA function similarly, and that both would  
11 have little to no impact on borderline-high TG patients in terms of LDL-C levels and would  
12 increase LDL-C levels in patients with very high TGs.

13 Defendants argue that a person of ordinary skill in the art “would have known that an  
14 increase in LDL-C was an adverse health effect to be avoided.” While an increase in LDL-C  
15 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that  
16 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3  
17 fatty acids generally, was related to increased conversion of VLDL to LDL particles.<sup>3944</sup>

18 Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the  
19 art would have been motivated, with a reasonable expectation of success, to administer a highly-  
20 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in

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22 <sup>3943</sup> See Section IV.

23 <sup>3944</sup> See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription  
24 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly  
converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride  
levels when given prescription omega-3 therapy”); Chan 2003.

1 LDL-C with DHA.” However, a person of ordinary skill in the art expected an increase in LDL-  
2 C in the very high TG population, with both EPA and DHA. It was well known at the time of  
3 the invention that omega-3 fatty acids, including both EPA and DHA, caused significant  
4 decrease in the production of VLDL particles and a significant increase in the conversion of  
5 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by  
6 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.<sup>3945</sup> A  
7 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering  
8 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering  
9 mechanism of omega-3 fatty acids.<sup>3946</sup> The discussion related to the TG-lowering mechanism of  
10 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.  
11 Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*  
12 reduce Apo-B<sup>3947</sup> (which is a reflection of total atherogenic lipoproteins)<sup>3948</sup> in very high TG  
13 patients, and accordingly would not have been motivated to administer the claimed EPA  
14 composition to the very high TG patient population.

15       Accordingly, a person of ordinary skill would not have been motivated to combine WO  
16 ‘118, WO ‘900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and  
17 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not  
18 have been motivated to combine WO ‘118 or WO ‘900, with the Lovaza PDR, or with Leigh-  
19 Firbank and/or Mori 2000.

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22 <sup>3945</sup> Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced  
decrease in VLDLs after n-3 fatty acid treatment”).

23 <sup>3946</sup> Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

24 <sup>3947</sup> *see* Section V.O.

<sup>3948</sup> *see* Section III.

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(2) Dependent Claims

(a) Defendants Have Not Shown that Claim 2 of the '920 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 2.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claim 2. Defendants contend, without providing any support, that the claim elements are the results of simply optimizing the conditions described in the prior art and within the purview of the skilled physicians. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. None of the cited references discloses administration of the claimed EPA to very high TG patients. Defendants further fail to explain how the cited references can be

1 combined to teach the administration of the claimed EPA to very high TG patients.<sup>3949</sup>  
2 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
3 considering other disclosures or even the reference as a whole. Each reference, however, must  
4 be evaluated for all that it teaches.<sup>3950</sup> Defendants’ unsupported cobbling of selective disclosures  
5 represents hindsight reconstruction.<sup>3951</sup>

6 Defendants fail to show a motivation or reason to combine or modify the references  
7 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
8 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not  
9 show why a person of ordinary skill would have been motivated to combine the references to  
10 achieve the claimed invention.<sup>3952</sup>

11 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
12 have successfully achieved the claimed invention. In fact, other than simply identifying prior art  
13 references that purportedly disclose disparate elements, Defendants do not even discuss whether  
14 a person of ordinary skill would have expected that the combination to work for its intended  
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18 <sup>3949</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 <sup>3950</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 <sup>3951</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 <sup>3952</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
23 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).  
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1 purpose.<sup>3953</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
2 claimed invention.

3 (b) Defendants Have Not Shown that Claim 3 of the  
4 ‘920 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
6 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
7 by clear and convincing evidence, they also have not adequately proven the obviousness of  
8 Claim 3.

9 Defendants contend, without providing meaningful support, that the claim element was  
10 well known in the art. These contentions: 1) do not assert what the prior art discloses to a  
11 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address  
12 whether the specific combination of claim elements were all present in the prior art references  
13 that would have been combined by a person of ordinary skill in the art to produce the claimed  
14 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*  
15 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
16 point of reading the element out of the claim. Although convenient and expedient, Defendants’  
17 approach does not conform with the Local Patent Rules of this District, the law of claim  
18 construction, or the law of obviousness.

19 Defendants fail to show a specific combination of references that discloses each element  
20 of the claimed invention. Defendants make a conclusory statement that the claimed method of

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23 <sup>3953</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 treatment was well known in the art, but such a naked assertion does not show why a person of  
2 ordinary skill would have been motivated to combine the references to achieve the claimed  
3 invention.<sup>3954</sup> Further Defendants cite to the “Lovaza product” without identifying the prior art  
4 reference to which they refer. Such a reference is inadequate.

5 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
6 have successfully achieved the claimed invention. Defendants do not even discuss whether a  
7 person of ordinary skill would have expected that the combination to work for its intended  
8 purpose.<sup>3955</sup> As such, Defendants fail to demonstrate reasonable expectation of success of the  
9 claimed invention.

10 (c) Defendants Have Not Shown that Claim 4 of the  
11 ‘920 Patent Would Have Been Obvious

12 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
13 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
14 by clear and convincing evidence, they also have not adequately proven the obviousness of  
15 Claim 4.

16 Defendants contend that it would be obvious that a person receiving the claimed EPA  
17 compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50  
18 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean  
19 LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for

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20 <sup>3954</sup>*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
21 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,  
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3955</sup>*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) fail to  
2 address whether the specific combination of claim elements were all present in the prior art  
3 references that would have been combined by a person of ordinary skill in the art to produce the  
4 claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie*  
5 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the  
6 point of reading the element out of the claim. Although convenient and expedient, Defendants'  
7 approach does not conform with the Local Patent Rules of this District, the law of claim  
8 construction, or the law of obviousness.

9 Defendants do not identify any combination of references. Because Defendants do not  
10 identify any combination of references, they necessarily fail to offer any evidence that a person  
11 of skill in the art would be motivated to combine those references in order to achieve the  
12 invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of  
13 ordinary skill would have been motivated to combine the elements, other than stating that a  
14 patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL  
15 would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously  
16 that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300  
17 mg/dL would be considered hypertriglyceridemic. Plaintiffs note that Defendants fail to provide  
18 specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. Defendants  
19 do not establish that a person of ordinary skill would have been motivated to combine the  
20 elements to achieve the claimed invention.<sup>3956</sup>

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22 <sup>3956</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).



1 Similarly, without the disclosure of a combination of references and a motivation/reason  
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
3 person of ordinary skill in the art would have had a reasonable expectation of success in  
4 achieving the claimed invention. Defendants do not even discuss whether a person of ordinary  
5 skill would have expected that the combination to work for its intended purpose for treating the  
6 recited patient population.<sup>3957</sup> As such, Defendants fail to demonstrate reasonable expectation of  
7 success of the claimed invention.

8 (d) Defendants Have Not Shown that Claim 5 of the  
9 ‘920 Patent Would Have Been Obvious

10 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
11 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
12 by clear and convincing evidence, they also have not adequately proven the obviousness of  
13 Claim 5.

14 Defendants do not identify any combination of references and simply provide a laundry  
15 list of references without explaining how each reference relates to the claimed invention.  
16 Defendants further contend, without any support, that a person of ordinary skill would have been  
17 able to determine the patient population in need of the claimed methods of treatment, would seek  
18 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat  
19 those patients having very high triglycerides regardless of the baseline values of these lipids.<sup>3958</sup>  
20 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
21 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific

22 <sup>3957</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically  
24 combined, but also that the combination would have worked for its intended purpose.”)

<sup>3958</sup> *Id.*

1 combination of claim elements were all present in the prior art references that would have been  
2 combined by a person of ordinary skill in the art to produce the claimed invention with a  
3 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
4 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
5 element out of the claim. Although convenient and expedient, Defendants' approach does not  
6 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
7 obviousness.

8 Defendants fail to show a specific combination of references that discloses each element  
9 of the claimed invention. Defendants merely list references, without reference to a specific page  
10 or section, that purportedly disclose disparate elements without explaining how they can be  
11 combined.<sup>3959</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
12 the claimed invention as a whole.<sup>3960</sup> Moreover, by simply identifying prior art references  
13 without discussing the specific teachings of each reference, Defendants fail to consider each  
14 prior art reference as a whole.<sup>3961</sup> Each reference must be evaluated for all that it teaches.  
15 Defendants' unsupported cobbling of selective disclosures represents hindsight  
16 reconstruction.<sup>3962</sup>

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18 <sup>3959</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

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20 <sup>3960</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

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22 <sup>3961</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit.”) (internal citation and quotation marks omitted).

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24 <sup>3962</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Because Defendants do not identify any combination of references, they necessarily fail  
2 to offer any evidence that a person of skill in the art would be motivated to combine those  
3 references in order to achieve the invention of the claim as a whole. Defendants make a  
4 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed  
5 methods of treatment, without providing a reason that would have prompted a person of ordinary  
6 skill to combine the elements.<sup>3963</sup> Such a naked assertion does not show why a person of  
7 ordinary skill would have been motivated to treat the recited patient population using the claimed  
8 methods of treatment.<sup>3964</sup>

9 Similarly, without the disclosure of a combination of references and a motivation/reason  
10 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
11 person of ordinary skill in the art would have had a reasonable expectation of success in  
12 achieving the claimed invention. In fact, other than simply identifying prior art references that  
13 purportedly disclose disparate elements, Defendants do not even discuss whether a person of  
14 ordinary skill would have expected that the combination to work for its intended purpose for  
15 treating the recited patient population.<sup>3965</sup> As such, Defendants fail to demonstrate reasonable  
16 expectation of success of the claimed invention.

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18 <sup>3963</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted)

21 <sup>3964</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3965</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

1 (e) Defendants Have Not Shown that Claims 6 and 7 of  
2 the '920 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
4 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
5 by clear and convincing evidence, they also have not adequately proven the obviousness of  
6 Claims 6 and 7.

7 Defendants contend, without support, that the recited reduction in TG represents  
8 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to  
9 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of  
10 ordinary skill to seek to reduce TG by the recited amount because there is no significance  
11 attached to the amount. Defendants conclude, without support, that there was a reasonable  
12 expectation of success without identifying any combination of references and without explaining  
13 how each reference relates to the claimed invention.<sup>3966</sup> These contentions: 1) do not assert  
14 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious  
15 analysis; 3) fail to address whether the specific combination of claim elements were all present in  
16 the prior art references that would have been combined by a person of ordinary skill in the art to  
17 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish  
18 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim  
19 element to the point of reading the element out of the claim. Although convenient and expedient,  
20 Defendants' approach does not conform with the Local Patent Rules of this District, the law of  
21 claim construction, or the law of obviousness.

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23 <sup>3966</sup> Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris\_Etherton 2002, Kurabayashi, Leigh-  
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney  
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,  
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Defendants further contend, without support, that a person of ordinary skill would  
2 “reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation  
3 containing no DHA,” as a formulation containing both EPA and DHA. Defendants conclude,  
4 without support, that it would have been obvious to administer a composition containing EPA,  
5 but containing no DHA, with a reasonable expectation of success in reducing triglycerides while  
6 avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to  
7 a person of ordinary skill in the art; 2) fail to address whether the specific combination of claim  
8 elements were all present in the prior art references that would have been combined by a person  
9 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of  
10 success; and 3) fail to establish *prima facie* obviousness. Defendants do not offer an obvious  
11 analysis, but trivialize the claim element to the point of reading the element out of the claim.  
12 Although convenient and expedient, Defendants’ approach does not conform with the Local  
13 Patent Rules of this District, the law of claim construction, or the law of obviousness.

14 Defendants do not identify any combination of references and simply provide a laundry  
15 list of references that purportedly disclose disparate elements without explaining how they can  
16 be combined.<sup>3967</sup> As such, Defendants discuss the claim elements in isolation, and fail to address  
17 the claimed invention as a whole.<sup>3968</sup> Defendants selectively cite to an unspecified isolated  
18 disclosure within a reference without considering other disclosures or even the reference as a  
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21 <sup>3967</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*  
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by  
demonstrating that each of its elements was, independently, known in the prior art”).

23 <sup>3968</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is  
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 whole. Each reference, however, must be evaluated for all that it teaches.<sup>3969</sup> Defendants’  
2 unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>3970</sup>

3 Because Defendants do not identify any combination of references, they necessarily fail  
4 to offer any evidence that a person of skill in the art would be motivated to combine those  
5 references in order to achieve the invention of the claim as a whole. Defendants make a  
6 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to  
7 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a  
8 person of ordinary skill to reduce triglycerides by the recited amount.<sup>3971</sup> Defendants’ burden to  
9 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”  
10 attached to the recited TG reduction amount.<sup>3972</sup> Defendants have not met the burden with the  
11 naked assertion that it would have been obvious to seek the claim element.

12 Similarly, without the disclosure of a combination of references and a motivation/reason  
13 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
14 person of ordinary skill in the art would have had a reasonable expectation of success in

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15 <sup>3969</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

16 <sup>3970</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
17 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

18 <sup>3971</sup> *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,  
20 1356-57 (Fed. Cir. 2007) (“While the KSR Court rejected a rigid application of the teaching, suggestion, or  
motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason  
21 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the  
claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.  
22 398, 418 (2007)).

23 <sup>3972</sup> Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been  
established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*  
24 case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

1 achieving the claimed invention. Defendants make a conclusory statement that there was a  
2 reasonable expectation of success, without providing a support other than merely identifying  
3 prior art references that purportedly disclose disparate elements.<sup>3973</sup> The mere fact that elements  
4 are capable of being physically combined does not establish reasonable expectation of  
5 success.<sup>3974</sup>

6 (f) Defendants Have Not Shown that Claim 8 of the  
7 '920 Patent Would Have Been Obvious

8 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
9 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
10 by clear and convincing evidence, they also have not adequately proven the obviousness of  
11 Claim 8.

12 Defendants offer no reference in support of their contention that this claims is obvious.  
13 Defendants contend, without providing any support, that it would be obvious to one of skill in  
14 the art to administer a composition containing EPA, but containing no DHA, with a reasonable  
15 expectation of success in reducing Apo-B levels. These contentions: 1) do not assert what the  
16 prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis;  
17 3) fail to address whether the specific combination of claim elements were all present in the prior  
18 art references that would have been combined by a person of ordinary skill in the art to produce  
19 the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima*

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21 <sup>3973</sup> *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be  
22 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational  
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.  
2006)) (internal quotation marks omitted).

23 <sup>3974</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”).

1 *facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element  
2 to the point of reading the element out of the claim. Although convenient and expedient,  
3 Defendants’ approach does not conform with the Local Patent Rules of this District, the law of  
4 claim construction, or the law of obviousness.

5 Defendants fail to show a specific combination of references that discloses each element  
6 of the claimed invention. None of the cited references discloses administration of the claimed  
7 EPA to very high TG patients. Defendants further fail to explain how the cited references can be  
8 combined to teach the administration of the claimed EPA to very high TG patients.<sup>3975</sup>  
9 Defendants selectively cite to an unspecified, isolated disclosure within a reference without  
10 considering other disclosures or even the reference as a whole. Each reference, however, must  
11 be evaluated for all that it teaches.<sup>3976</sup> Defendants’ unsupported cobbling of selective disclosures  
12 represents hindsight reconstruction.<sup>3977</sup>

13 Defendants fail to show a motivation or reason to combine or modify the references  
14 recited above. Defendants make a conclusory statement that the claimed methods of treatment  
15 would have been obvious but such a naked assertion does not show why a person of ordinary  
16 skill would have been motivated to combine the references to achieve the claimed invention.<sup>3978</sup>

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19 <sup>3975</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

20 <sup>3976</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 <sup>3977</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 <sup>3978</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill



1 Defendants fail to show a reasonable expectation that a person of ordinary skill would  
2 have successfully achieved the claimed invention. In fact, Defendants do not even discuss  
3 whether a person of ordinary skill would have expected that the combination to work for its  
4 intended purpose.<sup>3979</sup> As such, Defendants fail to demonstrate reasonable expectation of success  
5 of the claimed invention.

6 Defendants rely on only one reference in their invalidity contentions with respect to this  
7 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,  
8 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of  
9 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument  
10 and no support for their argument that Theobald makes such a disclosure. Defendants appear to  
11 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all  
12 atherogenic lipoproteins.<sup>3980</sup>

13 Defendants then make the unsupported assertion that “one of ordinary skill in the art  
14 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to  
15 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald  
16 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render  
17 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis  
18 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL  
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21 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
22 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 <sup>3979</sup> *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable  
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically  
combined, but also that the combination would have worked for its intended purpose.”)

<sup>3980</sup> June 26, 2012 Bays Declaration; *see also* Section III.

1 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with  
 2 respect to this claim or Apo-B levels.

3 As discussed above, *see* Section IV, Theobald discloses the administration of a  
 4 triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While  
 5 Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a  
 6 component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of  
 7 administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to  
 8 consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following  
 9 administration of the triacylglycerol composition of that reference.<sup>3981</sup>

10 **TABLE 3**  
 Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

	DHA		Placebo		Treatment effect <sup>1</sup>
	Before treatment	After treatment	Before treatment	After treatment	
Total cholesterol (mmol/L)	5.15 ± 0.145 <sup>2</sup>	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42) <sup>3</sup>
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38) <sup>4</sup>
HDL cholesterol (mmol/L) <sup>5</sup>	1.47 ± 0.052	1.55 ± 0.064	1.46 ± 0.062	1.48 ± 0.056	0.07 (0.005, 0.14)
Triacylglycerol (mmol/L) <sup>6</sup>	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	-0.18 (-0.37, 0.05)
<b>Apolipoprotein B (g/L)</b>	<b>0.84 ± 0.027</b>	<b>0.87 ± 0.026</b>	<b>0.83 ± 0.028</b>	<b>0.84 ± 0.028</b>	<b>0.03 (0.002, 0.055)<sup>7</sup></b>
LDL cholesterol:apo B (mmol/g)	3.75 ± 0.376	3.96 ± 0.462	3.74 ± 0.521	3.84 ± 0.409	0.12 (0.004, 0.24) <sup>3</sup>
Weight (kg) <sup>8</sup>	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (-0.85, 0.24)

<sup>1</sup> Mean difference between active treatment and placebo; 95% CI in parentheses.

<sup>2</sup>  $\bar{x} \pm$  SEM (all such values);  $n = 38$ .

<sup>3,4,7</sup> Paired  $t$  test: <sup>3</sup> $P = 0.04$ , <sup>4</sup> $P = 0.004$ , <sup>7</sup> $P = 0.03$ .

<sup>5</sup> HDL increased in subjects receiving DHA first. Significant treatment  $\times$  order effect,  $P = 0.005$ .

<sup>6</sup>  $n = 37$ ; data were log transformed before analysis by paired  $t$  test.

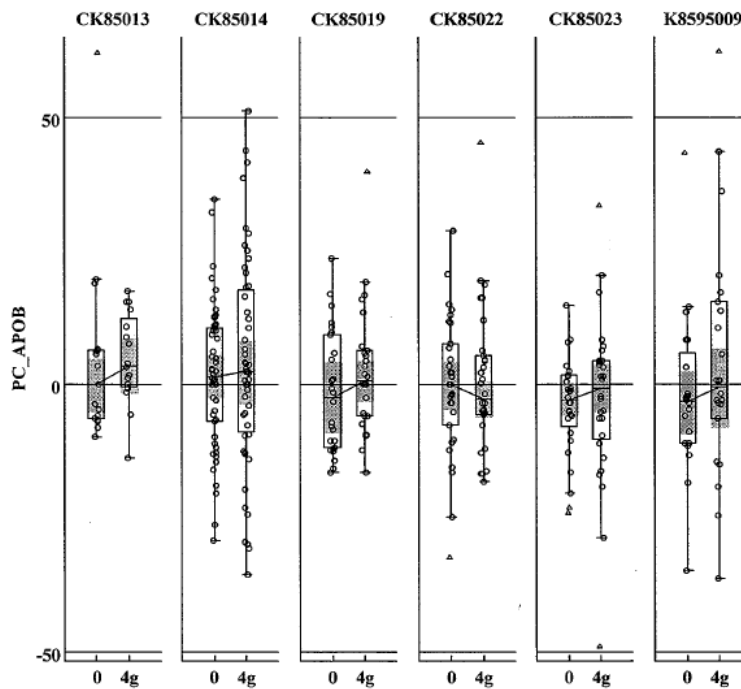
<sup>8</sup> Weight increased over the entire study period. Significant order  $\times$  time effect,  $P = 0.001$ .

18 As discussed above, *see* Section III, a person of skill in the art would not have  
 19 distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a  
 20 person of ordinary skill would have considered Theobald, they would not conclude from the  
 21 reference that EPA therapy decreases Apo-B levels in very high TG patients.

24 <sup>3981</sup> Theobald at 561, table 3.

1 A person of skill in the art would *not* have understood that EPA therapy in very high TG  
 2 patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked  
 3 to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on  
 4 Apo-B levels in patients with very high TG levels.<sup>3982</sup> The Lovaza clinical trial, which was a  
 5 large study conducted on patients with very high TG levels, shows no difference between a  
 6 placebo-control group and the treatment group with respect to Apo-B levels.<sup>3983</sup>

14. Box plot of individual Category I studies -% change of APOB



19 In each of these studies, including K8595009, where subjects had a median baseline TG  
 20 level of 818 mg/dL,<sup>3984</sup> there was no change in Apo-B between the control and treatment groups.

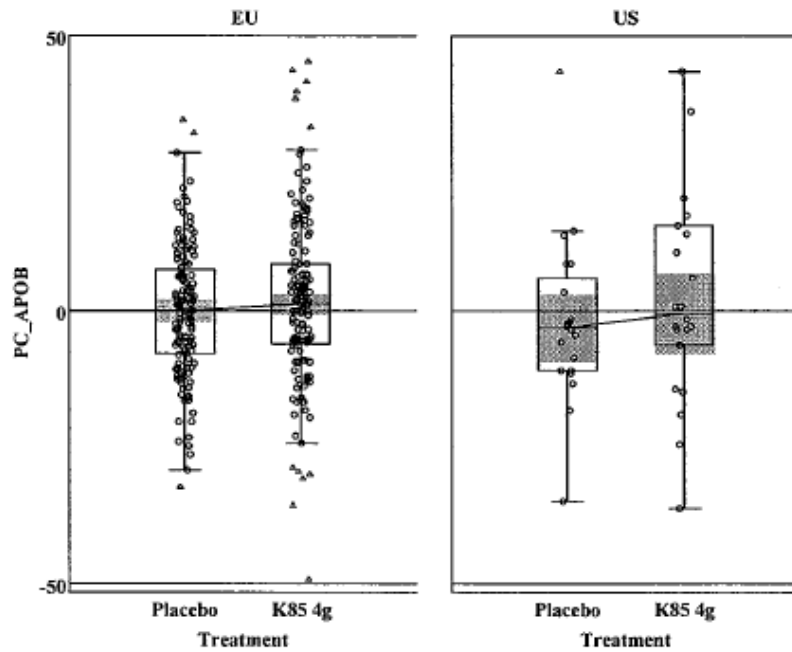
22 <sup>3982</sup> May 8, 2012 Bays Declaration.

23 <sup>3983</sup> Lovaza Approval Package at Table 14.

24 <sup>3984</sup> The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

1 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected  
2 that treatment with Lovaza did not impact Apo-B compared to placebo.<sup>3985</sup>

3  
4 7. Box plot of pooled Category I studies -% change of APOB



16 Indeed, none of the data reported in the Lovaza clinical trials reflects a decrease in Apo-  
17 B. In addition to the Lovaza studies, a person of ordinary skill would have understood that the  
18 literature reported, in a variety of clinical studies, that omega-3s do not impact Apo-B levels.<sup>3986</sup>  
19 While Theobald does not even support Defendants' obviousness arguments, their selective  
20 citation of that reference represents impermissible hindsight bias. The examiner had before him  
21 a large number of prior art references reporting Apo-B effects and, even as defendants concede,  
22

23 <sup>3985</sup> Lovaza Approval Package at Table 7.

24 <sup>3986</sup> See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 | agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of  
2 | those references, also reflecting a lack of motivation and no reasonable expectation of  
3 | success.<sup>3987</sup>

4 | Further, a person of skill in the art would have understood Apo-B to be a surrogate for the  
5 | number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.<sup>3988</sup> The person of  
6 | skill in the art would also have recognized that, as TG levels in patients with very high TG levels  
7 | rose, an increasing amount of TGs in those patients were contained within chylomicrons. As  
8 | discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic  
9 | lipoproteins, but instead smaller, denser particles referred to as remnant.<sup>3989</sup> Accordingly,  
10 | because very high TG patients had increasing levels of TGs stored in chylomicrons and because  
11 | chylomicron processing would not have been understood to yield changes in Apo-B, a person of  
12 | skill in the art would have believed that TG-lowering therapies directed to very high TG patients  
13 | would not significantly impact Apo-B.

14 | Accordingly, a person of ordinary skill in the art would not have been motivated to  
15 | replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art  
16 | have been motivated to administer the EPA composition of the claimed invention to very high  
17 | TG patients. For the same reasons, a person of ordinary skill in the art would not have a  
18 | reasonable expectation of success in achieving the claimed invention.

22 | \_\_\_\_\_  
<sup>3987</sup> Defendants' Contentions at 236.

23 | <sup>3988</sup> ATP-III at 3170; Bays 2008 I at 395.

24 | <sup>3989</sup> Kwiterovich in Kwiterovich at 4.

1 (g) Defendants Have Not Shown that Claim 9 of the  
2 '920 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
4 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
5 by clear and convincing evidence, they also have not adequately proven the obviousness of  
6 Claim 9.

7 Defendants contend that it would have been obvious to use the claimed composition to  
8 reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy.  
9 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in  
10 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific  
11 combination of claim elements were all present in the prior art references that would have been  
12 combined by a person of ordinary skill in the art to produce the claimed invention with a  
13 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants  
14 do not offer an obvious analysis, but trivialize the claim element to the point of reading the  
15 element out of the claim. Although convenient and expedient, Defendants' approach does not  
16 conform with the Local Patent Rules of this District, the law of claim construction, or the law of  
17 obviousness.

18 Defendants do not identify any combination of references. Because Defendants do not  
19 identify any combination of references, they necessarily fail to offer any evidence that a person  
20 of skill in the art would be motivated to combine those references in order to achieve the  
21 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of  
22 ordinary skill would have been motivated to combine the elements.<sup>3990</sup> As such, Defendants fail

23 <sup>3990</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the KSR  
24 Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry,

1 to demonstrate that there was no motivation to combine the references to achieve the claimed  
2 invention.

3 Similarly, without the disclosure of a combination of references and a motivation/reason  
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
5 person of ordinary skill in the art would have had a reasonable expectation of success in  
6 achieving the claimed invention. Defendants make conclusory statements without providing any  
7 support. What is more, Defendants do not even discuss the reasonable expectation of reducing  
8 VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of  
9 reducing VLDL-C levels using the claimed methods.

10 (h) Defendants Have Not Shown that Claim 10 of the  
11 '920 Patent Would Have Been Obvious

12 Plaintiffs incorporate by reference the discussion related to the Independent Claim in  
13 Section V.H.3. Because Defendants have not shown the obviousness of the Independent Claim  
14 by clear and convincing evidence, they also have not adequately proven the obviousness of  
15 Claim 10. Defendants also assert that “one of skill in the art would have been motivated, with a  
16 reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little  
17 to no DHA, in order to avoid the expected increase in LDL-C with DHA with a reasonable  
18 expectation of success.” As discussed above, these contentions are incorrect and contrary to  
19 what a person of ordinary skill would expect. Moreover, these contentions: 1) do not assert  
20 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious  
21 analysis; 3) fail to address whether the specific combination of claim elements were all present in

22  
23 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 the prior art references that would have been combined by a person of ordinary skill in the art to  
2 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish  
3 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim  
4 element to the point of reading the element out of the claim. Although convenient and expedient,  
5 Defendants' approach does not conform with the Local Patent Rules of this District, the law of  
6 claim construction, or the law of obviousness.

7 Defendants do not identify any combination of references. Because Defendants do not  
8 identify any combination of references, they necessarily fail to offer any evidence that a person  
9 of skill in the art would be motivated to combine those references in order to achieve the  
10 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of  
11 ordinary skill would have been motivated to combine the elements.<sup>3991</sup> As such, Defendants fail  
12 to demonstrate that there was no motivation to combine the references to achieve the claimed  
13 invention.

14 Similarly, without the disclosure of a combination of references and a motivation/reason  
15 to combine or modify the references, Defendants necessarily fail to offer any evidence that a  
16 person of ordinary skill in the art would have had a reasonable expectation of success in  
17 achieving the claimed invention. Defendants make conclusory statements without providing any  
18 support. What is more, Defendants do not even discuss the reasonable expectation of reducing  
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22 <sup>3991</sup> *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*  
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,  
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill  
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness  
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).



1 LDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of  
2 reducing LDL-C levels using the claimed methods.

3 Defendants further allege that the effects on LDL-C represent “properties inherent upon  
4 administering a formulation known in or rendered obvious by the prior art.” Defendants do not  
5 identify any prior art that shows that the effects on LDL-C was an inherent property of a pure  
6 EPA composition. Moreover, any inherent property that was not readily known in the art may  
7 not show obviousness because “[t]hat which may be inherent is not necessarily known; [and]  
8 obviousness cannot be predicated on what is unknown.”<sup>3992</sup>

9 **4. The '920 Patent is Not Invalid Under § 112**

10 a) Defendants Have Not Demonstrated that the Claims of the '920  
11 patent Are Invalid for Indefiniteness

12 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]  
13 the subject matter which the applicant regards as his invention.”<sup>3993</sup> Patent claims are valid in  
14 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the  
15 art about the scope of the invention” in light of the specification and the prosecution history.<sup>3994</sup>  
16 The Supreme Court has recognized that “absolute precision is unattainable” in claim language  
17 and “the certainty which the law requires in patents is not greater than is reasonable.”<sup>3995</sup>  
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<sup>3992</sup> *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993).

20 <sup>3993</sup> Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and  
21 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite  
22 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions  
other than by making conclusory assertions in return. Therefore, Defendants should be precluded from  
supplementing their naked assertions with new basis in the course of the litigation.

23 <sup>3994</sup> *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

24 <sup>3995</sup> *Id.* at 2129.

1 Defendants allege that a number of terms containing the phrases “about” and  
2 “substantially” are indefinite. Defendants do not provide any reason why these terms are  
3 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,  
4 these terms are routinely used in patent claims, and are not *per se* indefinite.<sup>3996</sup> In particular,  
5 courts have held repeatedly that claims that contain the words “about” and “substantially” are not  
6 indefinite.<sup>3997</sup> Here, a person of ordinary skill would understand with reasonable certainty what  
7 is claimed when the claims are read in light of the specification and prosecution history.<sup>3998</sup>  
8 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being  
9 indefinite.

10 Defendants further allege that the term “4g per day of a pharmaceutical composition  
11 comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” is  
12 indefinite. They contend that, because there is no indication of how much of the pharmaceutical  
13 composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid  
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15 <sup>3996</sup> *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms  
16 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the  
17 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.  
18 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the  
19 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d  
20 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe  
21 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish  
22 the claimed subject matter from the prior art, it is not indefinite.”).

23 <sup>3997</sup> *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim  
24 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.  
2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction  
“define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy  
Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration  
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,  
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not  
indefinite).

<sup>3998</sup> *See generally* the ’920 patent and its prosecution history.

1 is present in the composition. This is incorrect. A claim can use a ratio to define amounts of  
2 components in a product, using terms such as “percent by weight.”<sup>3999</sup> In light of the  
3 specification and prosecution history, a person of ordinary skill would understand with  
4 reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the  
5 recited pharmaceutical composition in relation to all fatty acids present.<sup>4000</sup> Therefore, these  
6 terms are not indefinite and do not render the claims indefinite.

7 Defendants further allege that the term “compared to baseline” is indefinite. Defendants,  
8 again, provide no basis for this allegation. In light of the specification and the prosecution  
9 history, a person of ordinary skill would know with reasonable certainty the scope of the term  
10 “compared to baseline” and therefore does not render the claims indefinite.<sup>4001</sup>

11 Finally, Defendants contend that the asserted claims improperly mix methods and  
12 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that  
13 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness  
14 analysis is based on what the claim language informs a person of ordinary skill in the art in light  
15 of the specification and the prosecution history. Defendants do not identify any actual claim  
16 language that mixes methods and formulations. Moreover, contributory infringement may be  
17 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*  
18 *process . . . knowing the same to be especially made or especially adapted for use in an*  
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20 <sup>3999</sup> *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at \*5–6 (D.N.J.  
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a  
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at \*10 (E.D. Tex. Apr. 27,  
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total  
volume of the solution, with this ratio expressed as a percentage”).

23 <sup>4000</sup> See generally the ’920 patent and its prosecution history.

24 <sup>4001</sup> See generally the ’920 patent and its prosecution history.

1 infringement of such patent.”<sup>4002</sup> Plaintiffs assert that Defendants’ ANDA products will be used  
2 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound  
3 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are  
4 mistaken and the ’920 patent claims are not indefinite for improperly mixing methods and  
5 formulations.

6 b) Defendants Have Not Demonstrated that the Claims of the ’920  
7 patent Are Invalid for Insufficient Written Description

8 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a  
9 written description of the invention.” This requires that the specification “reasonably convey”  
10 that the applicant “invented” or “had possession” of the claimed subject matter when the  
11 application was filed.<sup>4003</sup> Support need not be literal<sup>4004</sup>—it may be implicit<sup>4005</sup> or inherent<sup>4006</sup> in  
12 the disclosure. In addition, it is unnecessary to include information that is already known or  
13 available to persons of ordinary skill.<sup>4007</sup>

14 Defendants make three arguments regarding the written description requirement. First,  
15 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack  
16 written description. This is incorrect. The specification of asserted patents literally discloses the  
17

18 \_\_\_\_\_  
<sup>4002</sup> 35 U.S.C. § 271(c) (emphasis added).

19 <sup>4003</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

20 <sup>4004</sup> *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d  
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

21 <sup>4005</sup> *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866  
F.2d at 424–25.

22 <sup>4006</sup> *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

23 <sup>4007</sup> *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,  
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

1 | claimed invention.<sup>4008</sup> Moreover, the recited baseline TG levels of the claimed invention appear  
2 | in the original claims of the application to which the asserted patent claims priority. Thus, there  
3 | is a strong presumption that the claimed invention is adequately described.<sup>4009</sup> Defendants do  
4 | not and cannot rebut this presumption. Specifically, the patient population is originally claimed  
5 | as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500  
6 | mg/dl.”<sup>4010</sup> The asserted claims recite the same patient population. Defendants do not contend  
7 | that the patient population of the asserted claims is not literally described by the specification  
8 | and in the original claims of the application to which the asserted patent claims priority. In fact,  
9 | the specification and the provisional patent application claims at the time of filing described  
10 | these limitations.<sup>4011</sup> Therefore, Defendants have failed to explain whether and how an aspect of  
11 | the claimed invention has not been described with sufficient particularity such that one skilled in  
12 | the art would recognize that the applicant had possession of the claimed invention.

13 |         Second, Defendants contend that “a person of skill in the art would not understand that  
14 | the inventor was in possession of a method incorporating [] specific dosages and quantities.”  
15 | Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the  
16 | dosages and quantities of the claimed methods.<sup>4012</sup> Moreover, the dosages and quantities of the  
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18 | <sup>4008</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
19 | inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);  
*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite  
20 | legal foundation for claiming that species.”).

21 | <sup>4009</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the  
22 | initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure  
23 | a description of the invention defined by the claims”).

24 | <sup>4010</sup> See U.S. Application No. 12/702,889.

<sup>4011</sup> See e.g., ‘920 patent at 13:29-34; 14:49-51; U.S. Application No. 12/702,889.

<sup>4012</sup> *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective  
inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);

1 method appear in the claims, as originally filed. Thus, there is a strong presumption that the  
2 claimed invention is adequately described.<sup>4013</sup> Defendants do not and cannot rebut this  
3 presumption. For example, the dosage of the composition was originally claimed as “about 1 g  
4 to about 4g.”<sup>4014</sup> The asserted claims recite “4 g.” Defendants do not contend that dosages and  
5 quantities of the asserted claims are not literally described by the specification and in the original  
6 claims. In fact, the specification and the provisional patent application claims, at the time of  
7 filing, described these limitations. Therefore, Defendants have failed to explain whether and  
8 how an aspect of the claimed invention has not been described with sufficient particularity such  
9 that one skilled in the art would recognize that the applicant had possession of the claimed  
10 invention.

11 Third, Defendants contend that “a person of skill in the art would not understand that the  
12 inventor was in possession of a method comprising a comparison against a second subject or  
13 against a second population.” The specification demonstrates that the applicants were in  
14 possession of the claimed inventions. For example, a person of ordinary skill would have  
15 understood that the inventor was in possession of a method comprising administration of a  
16 composition with the recited properties, based on a comparison of a subject or a population  
17 against a second subject, baseline, or a second population.

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*Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite legal foundation for claiming that species.”).

<sup>4013</sup> *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims”).

<sup>4014</sup> See U.S. Provisional Application No. 61/151,291.

1 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,<sup>4015</sup>  
2 the court elaborated that “possession” means possession as evidenced by disclosure. In this case,  
3 the specification of asserted patents literally disclose the claimed invention in the specification  
4 and the claims as originally filed. Thus, an examination of the four corners of the specification  
5 from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the  
6 asserted patents were in possession of the claimed invention.

7 Defendants conclude by alleging that the specification does not describe anything more  
8 than what is obvious, and thus does not provide adequate support for any nonobvious claim.  
9 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the  
10 specification; nonobviousness can be supported by post-filing date evidence for example.<sup>4016</sup>  
11 Written description requires only that the specification reasonably conveys that the applicant had  
12 possession of the claimed subject matter when the application was filed. Therefore, whether the  
13 claims are obvious has no bearing on the adequacy of written description.

14 c) Defendants Have Not Demonstrated that the Claims of the ‘920  
15 patent Are Invalid for Lack of Enablement

16 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person  
17 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would  
18 require undue experimentation for a person of ordinary skill to make or use the invention.

19 <sup>4015</sup> *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 <sup>4016</sup> See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)  
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is  
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those  
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,  
24 1307 (Fed. Cir. 2011) (“[E]vidence of unexpected results may be [considered] ... even if that evidence was obtained  
after the patent's filing or issue date.”); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir.  
2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full  
range of an invention is not always achieved at the time of filing the patent application.”).

1 Factors that may be considered include the quantity of experimentation necessary, the amount of  
2 direction or guidance presented, the presence or absence of working examples, the nature of the  
3 invention, the state of the prior art, the relative skill of those in the art, the predictability or  
4 unpredictability of the art, and the breadth of the claims.<sup>4017</sup> The enablement requirement is  
5 separate and distinct from the written description requirement,<sup>4018</sup> and as such a claim does not  
6 require descriptive support in the disclosure as originally filed for it to be enabled.<sup>4019</sup>

7 Defendants make two specific arguments regarding the enablement requirement. First,  
8 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of  
9 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the  
10 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary  
11 skill would be able to determine the amounts of the components in the pharmaceutical  
12 composition without any experimentation, much less undue experimentation.

13 Second, Defendants contend that it would take undue experimentation to obtain the  
14 claimed required results listed in the full scope of the patent claims, including the claimed lipid  
15 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed  
16 method and certainly not undue experimentation. Administration of a recited amount of a recited  
17 composition, for a recited duration, to a specific, recited patient population produces the recited  
18 results. No additional experimentation is required, and Defendants do not explain their  
19 allegation that undue experimentation would be required. Defendants also do not contend that  
20 following the claimed method (each recited element) does not produce the recited results. The  
21

22 \_\_\_\_\_  
<sup>4017</sup> See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 <sup>4018</sup> *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 <sup>4019</sup> MPEP § 2164.



1 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly  
2 demonstrate that administration of EPA of the recited composition, when administered to  
3 patients with very high TG levels for at least 12 weeks, as specified, produces the recited  
4 results.<sup>4020</sup> Therefore, the claims are not invalid for lack of enablement.

5 Defendants conclude by alleging that the specification does not enable anything more  
6 than what is obvious over the prior art or was known to a person of skill in the art. First,  
7 Defendants do not cite any case or present a legal theory to support this assertion. As such, they  
8 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be  
9 precluded in the future from raising any new legal theory to support this assertion. Moreover,  
10 while the '920 patent's specification enables a person of ordinary skill to obtain the claimed  
11 limitations without undue experiment, the claimed limitations would not have been obvious to a  
12 person of ordinary skill, as discussed in Section V.H.3. Furthermore, Plaintiffs have initiated  
13 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its  
14 claimed methods.<sup>4021, 4022</sup> Therefore, a person of ordinary skill would have concluded that the  
15 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

16 I. **The '560 Patent**

17 1. **The '560 Patent Claims Eligible Subject Matter Under § 101**

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21 <sup>4020</sup> See VASCEPA® Prescribing Information at Table 2.

22 <sup>4021</sup> *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any  
23 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical  
24 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that  
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

<sup>4022</sup> See May 16, 2011 Bays Declaration at Appendix B.

1 Defendants' allegation that the asserted claims of the '560 patent relate to ineligible  
2 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*  
3 case under Section 101 or provide a legal or factual basis to support their allegations.

4 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local  
5 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be  
6 provided.<sup>4023</sup> The bare assertion of invalidity under Section 101 without providing the grounds  
7 for such an allegation and examining the elements of the asserted claims of the '560 patent does  
8 not meet this requirement and thwarts the purpose of the Rules.<sup>4024</sup>

9 The inquiry under Section 101 involves a two-step test: first, a court must determine  
10 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical  
11 phenomenon, or abstract idea.<sup>4025</sup> Second, even if the claim is directed to one of these concepts,  
12 it still may be patent eligible and the court must determine what else is part of the claim.<sup>4026</sup>

13 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*  
14 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of  
15 the '560 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and]

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17 <sup>4023</sup> See Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all  
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed  
statement of any grounds of invalidity based on 35 U.S.C. § 101.").

19 <sup>4024</sup> Nor does the preceding paragraph, which provides only a purported summary of the claims of the '560 patent, or  
subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the  
20 grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,*  
*Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) ("The District of Nevada's Local Patent  
21 Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide  
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those  
contentions when new information comes to light in the course of discovery") (internal quotation marks omitted).

22 <sup>4025</sup> *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) ("First, we determine whether the claims at  
23 issue are directed to one of those patent-ineligible concepts.").

24 <sup>4026</sup> *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?").

1 conventional” steps, and the only novel element related to administering the proper dosage based  
2 on a natural law observation.<sup>4027</sup> However, the claims merely recited this natural law without  
3 reciting any novel application of it.<sup>4028</sup> The Court found that providing protection to such  
4 claims would result in pre-empting “a broad range of potential uses” and excluding others from  
5 using “the basic tools of scientific and technical work.”<sup>4029</sup> A method of treatment claim,  
6 specifying the subjects, dosage levels, composition, and time course does not raise the concerns  
7 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent  
8 protection.<sup>4030</sup>

9 Defendants suggest that the recited EPA composition of each asserted claim is a naturally  
10 occurring substance. It is not. Even references contained within Defendants’ own contentions  
11 make clear that EPA of the requisite purity and characteristics is not found in nature.<sup>4031</sup> As  
12 expressed by the patents cited in Defendants’ contentions and well-established precedent, for  
13 decades it has been accepted that compositions isolated from nature or purified beyond their  
14 natural state are patent-eligible.<sup>4032</sup> Moreover, Defendants’ assertions are immaterial to a Section  
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16 <sup>4027</sup> *Mayo*, 132 S. Ct. at 1294.

17 <sup>4028</sup> *Id.* at 1301.

18 <sup>4029</sup> *Id.*

19 <sup>4030</sup> *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way  
20 of using an existing drug); *see also* *Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability  
21 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula  
and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d  
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent  
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

22 <sup>4031</sup> *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative  
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidation Contentions, *e.g.*, at 26–27).

23 <sup>4032</sup> *See, e.g.*, *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394  
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

1 101 defense because method of treatment claims like the ones asserted in this case are patent  
2 eligible even if they are directed to administration of a naturally occurring substance.<sup>4033</sup>

3 To the extent Defendants are arguing that a law of nature both underlies the claims and  
4 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the  
5 claimed effects are the natural result of ingesting a naturally-occurring substance.”<sup>4034</sup> Since the  
6 composition that is the subject of the claims is not naturally occurring, Defendants appear to  
7 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states  
8 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad  
9 characterization of laws of nature.<sup>4035</sup> To say that the claims of the ’560 patent claim a law of  
10 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode  
11 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to  
12 underlying principles of nature” that would “make all inventions unpatentable.”<sup>4036</sup> Indeed, even  
13 those concerned about the implications of *Mayo* on future patents were focused on diagnostic  
14 claims not treatment claims of the type that *Mayo* stated were typical and patentable.<sup>4037</sup>

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17 <sup>4033</sup> *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

18 <sup>4034</sup> See Defendants’ Joint Invalidity Contentions at 567.

19 <sup>4035</sup> See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes  
20 to achieve a desired outcome . . . . That one way of describing the process is to describe the natural ability of the  
21 subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we  
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability  
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to  
aspirin).”).

22 <sup>4036</sup> See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

23 <sup>4037</sup> See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying  
24 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,  
particularly in the area of diagnostic research.”).

1 Even if there is some underlying law of nature in the asserted claims, the subject matter  
2 of the '560 patent remains eligible for protection under Section 101. As articulated by *Mayo* and  
3 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to  
4 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to  
5 foreclose from others the use of that equation in conjunction with all of the other steps in their  
6 claimed process.’”<sup>4038</sup> As discussed above, the asserted claims of the '560 patent contain a  
7 novel, unconventional, and specific method of treatment comprising a particularized application  
8 of a nonnaturally occurring substance and does not preempt the use of a law of nature.<sup>4039</sup>

9 Defendants also argue that any argument by Amarin in response to Defendants’ § 112  
10 arguments are further evidence of invalidity under § 101. This argument is without merit. The  
11 claims are enabled and written description is satisfied for the reasons discussed below. In  
12 addition, as discussed above, the asserted claims are not merely a naturally-occurring  
13 phenomena, and thus satisfy the requirements of § 101.

14 **2. The Asserted Claims of the ‘560 Patent Are Not Anticipated by WO**  
15 **‘118**

16 To anticipate, a single prior art reference must sufficiently describe a claimed invention  
17 so that the public is in “possession” of that invention.<sup>4040</sup> Therefore, to anticipate, a reference  
18 must set forth every element of the claim, either expressly or inherently, in as complete detail as  
19  
20

21 <sup>4038</sup> See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

22 <sup>4039</sup> See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at \*4 (C.D. Cal. July 24, 2012)  
23 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was  
24 “just one step in the whole process” claimed by the invention).

<sup>4040</sup> *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

1 is contained in the claim.<sup>4041</sup> The claim elements must also be “arranged” in the prior art  
2 reference, just as they are in the claim,<sup>4042</sup> rather than as “multiple, distinct teachings that the  
3 artisan might somehow combine to achieve the claimed invention.”<sup>4043</sup> In addition, public  
4 “possession” requires that the prior art enable a person of ordinary skill to make and use the  
5 invention without undue experimentation.<sup>4044</sup> Factors that may be included in this analysis  
6 include the quantity of experimentation necessary, the amount of direction or guidance  
7 presented, the presence or absence of working examples, the nature of the invention, the state of  
8 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,  
9 and the breadth of the claims.<sup>4045</sup> This inquiry is objective, and thus evidence of undue  
10 experimentation need not be prior art.<sup>4046</sup>

11 Defendants assert that Claims 1-20 of the ’560 Patent are anticipated by the WO ‘118  
12 reference.<sup>4047</sup>

13 A element-by-element analysis, identifying each element of each asserted claim that is  
14 absent from WO ‘118, is provided below. The contentions below are incorporated by reference  
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16 <sup>4041</sup> *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.  
Cir. 1989).

17 <sup>4042</sup> *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

18 <sup>4043</sup> *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587  
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

19 <sup>4044</sup> *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,  
Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

20 <sup>4045</sup> *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

21 <sup>4046</sup> *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999  
F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.  
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822  
F.2d 1074, 1078 (Fed. Cir. 1987).

22 <sup>4047</sup> References to “WO ’118” are to the English translation that was filed with the European application. Plaintiffs  
23 reserve their right to obtain a certified translation of WO ‘118.

24

1 into Exhibit I, and vice-versa. WO '118 does not anticipate the claims of the '560 patent because  
2 it does not describe, properly arrange, or enable the '560 patent claims.

3 a) WO '118 Does Not Teach Every Element of the Claims of the  
4 '560 Patent

5 (1) WO '118 Does Not Describe the Claimed Lipid Effects

6 It is well established that, for a prior art reference to anticipate, “every element of the  
7 claimed invention must be identically shown in a single reference.”<sup>4048</sup> Moreover, the elements  
8 of the claimed invention must have “strict identity” with the elements of the reference; “minimal  
9 and obvious” differences are sufficient to prevent anticipation.<sup>4049</sup> Here, WO '118 entirely fails  
10 to disclose the following elements of Claim 1 of the '560 Patent: *to effect a reduction in*  
11 *triglycerides in the subject*. WO '118 further entirely fails to disclose the following elements of  
12 Claim 11 of the '560 Patent: *to effect a reduction in triglycerides in the subject compared to*  
13 *placebo control*. Defendants appear to concede that WO '118 does not expressly teach these  
14 elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.<sup>4050</sup>  
15 Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this  
16 element because WO '118 does not.

17 Instead, Defendants argue that these elements express the intended result of a method that  
18 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth  
19 below, WO '118 fails to disclose each element of the independent claims of the '560 Patent,  
20 either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method.  
21 Defendants also argue that these elements represent inherent, natural properties of EPA, and are

22 <sup>4048</sup> *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v.*  
*Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

23 <sup>4049</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 <sup>4050</sup> Defendants' Invalidation Contentions at 202-204.

1 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of  
2 anticipation and claim construction. Further, while Defendants argue that the inherent properties  
3 are exemplified in the prior art, they fail to identify even a single prior art reference that makes  
4 such a disclosure. Defendants cannot point to a single, specific prior art reference because the  
5 claimed pharmaceutical composition has never been administered in the manner claimed to the  
6 claimed patient population. Also, these elements are positively recited in the body of the claim  
7 and therefore cannot be construed as a non-limiting preamble and must be given patentable  
8 weight.

9 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid  
10 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
11 inherently anticipate as a matter of law.”<sup>4051</sup> “[A]nticipation by inherent disclosure is appropriate  
12 only when the reference discloses prior art that must *necessarily* include the unstated  
13 limitation.”<sup>4052</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
14 possibly present’ in the prior art.”<sup>4053</sup> WO ‘118 fails to provide any data related to the lipid  
15 effects of the disclosed invention on patients described in the publication. Therefore, Defendants  
16 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets  
17 the elements of the independent claims every time it is administered.

18 Defendants fail to demonstrate that administration of the claimed EPA compositions  
19 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants  
20 suggests that EPA administration may increase LDL-C.<sup>4054</sup> Rambjor is a clinical study which

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22 <sup>4051</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>4052</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 <sup>4053</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

<sup>4054</sup> *See, e.g., Rambjor.*



1 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA  
2 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a  
3 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*  
4 decrease TG without increasing LDL-C *every time it is administered*.

5 Therefore, WO '118 cannot anticipate the independent claims of the '560 patent.  
6 Because the dependent claims include all of the claim elements of the independent claims, WO'  
7 118 cannot anticipate any of the dependent claims as well.

8 (2) WO '118 Does Not Disclose Methods of Treating The  
9 Claimed Patient Population

10 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition  
11 be administered in the manner claimed to the claimed patient population. Defendants attempt to  
12 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is  
13 the introductory clause of a patent claim and includes everything from the beginning of the claim  
14 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the  
15 preamble.

16 A claim preamble has patentable weight if, “when read in the context of the entire claim,  
17 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,  
18 and vitality’ to the claim.”<sup>4055</sup> Additionally, the preamble constitutes a claim element when the  
19 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and  
20 claim body to define the claimed limitation.”<sup>4056</sup>

21 The preamble of the asserted claims is limiting for several reasons. The term “subject” in  
22 the preamble of the independent claims defines and provides antecedent basis for the “subject”

23 <sup>4055</sup> *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

24 <sup>4056</sup> *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

1 recited in the body of the claims. When reading the claim, one must rely on both the preamble  
2 and the claim body to define the claimed invention.

3 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is  
4 properly construed as a limitation of the claim itself.”<sup>4057</sup> The recitation of a “method of  
5 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing  
6 triglycerides in the body of the claim and emphasizes the intentional purpose for which the  
7 method must be performed - to reduce triglycerides.

8 It is clear that “the claim drafter chose to use both the preamble and the body of the claim  
9 to define the subject matter of the claimed invention.”<sup>4058</sup> Thus, the entire preamble in the  
10 independent claims of the ‘560 must contain patentable weight.

11 WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims.  
12 WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be  
13 administered in the manner claimed to the claimed patient population.

14 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,  
15 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**  
16 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the  
17 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence  
18 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and  
19 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden  
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21 <sup>4057</sup> *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*  
22 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases  
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a  
24 necessary and defining aspect of the invention, specifically its portability,” and because the specification and  
prosecution history “emphasize this feature of the invention”).

<sup>4058</sup> *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest  
2 angina and exercise-induced angina, and destabilization of the angina.”<sup>4059</sup> The invention of WO  
3 ‘118 is intended to be administered to any person in need of prevention of the occurrence of  
4 cardiovascular events, who are typically hypercholesterolemia patients.<sup>4060</sup> WO ‘118 does not  
5 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot  
6 anticipate the independent claims.

7 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail  
8 to prove that these elements of the claimed invention have “strict identity” with the elements of  
9 the reference.<sup>4061</sup> WO ‘118 fails to anticipate this claim element because the broad disclosure  
10 fails to anticipate the narrow claimed range, and the specific patient population defined in the  
11 claims is an essential part of the claimed invention.

12 There is no evidence in that subject as described in the claims were ever treated. In fact,  
13 WO ‘118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the  
14 definition of “hypertriglyceridemia” in WO ‘118 to argue that WO ‘118 discloses treatment of  
15 the subject as described in the claims. It does not. Defendants’ argument rests on the definition  
16 in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150  
17 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working  
18 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels  
19 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any  
20 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as

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22 <sup>4059</sup> WO ‘118 at 12.

23 <sup>4060</sup> *Id.*

24 <sup>4061</sup> *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 evidence that a “person of ordinary skill in the art would have understood that the term  
2 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of  
3 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable  
4 and then merely provides examples of commercially available “soft capsules,” such as Omacor.  
5 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients  
6 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be  
7 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’  
8 or ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”<sup>4062</sup> Therefore,  
9 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO  
10 ‘118 meets the claim elements of the independent claims every time it is administered.

11 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges  
12 claimed by the ‘560 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500  
13 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between  
14 330 and 450 degrees. The court found that the broader prior art range could not anticipate the  
15 claimed temperature range, “[g]iven the considerable difference between the claimed range and  
16 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the  
17 claimed range with sufficient specificity to anticipate this element of the claim.”<sup>4063</sup> A prior art’s  
18 teaching of a broad genus does not necessarily disclose every species within that genus. The  
19 court explained the slightly overlapping range between the preferred range and claimed range “is  
20 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>4064</sup> and therefore

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<sup>4062</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>4063</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

24 <sup>4064</sup> *Atofina*, 441 F.3d at 1000.

1 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of  
2 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not  
3 anticipate the subject as described in the claims because it fails to described the claimed TG  
4 range with sufficient specificity.

5 The court in *Atofina* ruled on an additional question of anticipation that also involved a  
6 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as  
7 compared to the patent’s claimed range of 0.1 to 5.0 percent.<sup>4065</sup> The court explained that  
8 “although there is a slight overlap, no reasonable fact finder could determine that this overlap  
9 describes the entire claimed range with sufficient specificity to anticipate this limitation of the  
10 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”<sup>4066</sup> Similarly,  
11 although there may be overlap between the definition of hypertriglyceridemia taught by WO  
12 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not  
13 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500  
14 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of  
15 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels  
16 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic  
17 events as the primary clinical objective),<sup>4067</sup> WO ‘118, therefore, does not expressly disclose the  
18 specific patient population that is an essential element of the claims of the asserted patents.  
19 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

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<sup>4065</sup> *Id.*

23 <sup>4066</sup> *Id.*

24 <sup>4067</sup> *See* Section III.

1           The treatment of a patient with elevated TG levels varies depending on their serum  
2 triglyceride levels. Identification of the patient population with very high TG levels (at least 500  
3 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,  
4 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment  
5 of lipid disorders.<sup>4068</sup> The ATP-III divided hypertriglyceridemia patients into three classes based  
6 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),  
7 and very-high TGs ( $\geq 500$  mg/dL)—and recommended substantially different treatment  
8 strategies for patients depending on classification.<sup>4069</sup> For the borderline-high and high TG  
9 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.<sup>4070</sup>  
10 Accordingly, in these populations, physicians focused on lowering LDL-C.<sup>4071</sup> In this patient  
11 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.  
12 In contrast, the primary goal for very-high TG patients ( $\geq 500$  mg/dL) was to reduce the risk of  
13 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated  
14 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary  
15 treatment goal.<sup>4072</sup> Therefore, as evidenced by the ATP-III, patients with very-high TG levels  
16 were considered fundamentally different from patients with borderline-high or high TGs from a  
17 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

18           Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride  
19 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In  
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21 <sup>4068</sup> *Id.*

22 <sup>4069</sup> ATP III at 3335; *See also* Section III.

23 <sup>4070</sup> *Id.*

24 <sup>4071</sup> *Id.*

<sup>4072</sup> *Id.*

1 fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at  
2 all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular  
3 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).  
4 Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels  
5 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by  
6 decreasing triglycerides), as required by the independent claims of the asserted patents, and  
7 therefore cannot anticipate the independent claims of the '560 Patent.

8 (3) WO '118 Does Not Describe the Claimed Pharmaceutical  
9 Composition or its Specific Administration

10 WO '118 further does not anticipate the claims of the '560 patent because it does not  
11 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as  
12 claimed, it cannot anticipate oral administration to the claimed "subject."

13 WO '118 additionally cannot anticipate the claims of the '560 patent because it does not  
14 disclose administering the pharmaceutical composition at a dose of about 4g per day.

15 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is  
16 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which  
17 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more  
18 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8  
19 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is  
20 not particularly limited as long as the intended effect, preventing the occurrence of  
21 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose  
22 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be  
23 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no  
24 working examples, data or other reference in WO '118 indicating that any subject (much less

1 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the  
2 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

3 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of  
4 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The  
5 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic  
6 range of 330 to 450 °C,”<sup>4073</sup> and therefore failed to anticipate the claimed range. The court in  
7 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate  
8 the patent’s claimed range of 0.1 to 5.0 percent.<sup>4074</sup> The court explained that “although there is a  
9 slight overlap, no reasonable fact finder could determine that this overlap describes the entire  
10 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are  
11 different, not the same. . . . Thus, there is no anticipation.”<sup>4075</sup> Similarly, although there may be  
12 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘560  
13 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range  
14 claimed by the ‘560 patent does not fall within WO ‘118’s preferred range. Defendants  
15 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,  
16 the example indicates that up to 900 mg of the EPA composition could be used three times per  
17 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘560  
18 patent and cannot anticipate the independent claims of the ‘560 Patent.

19 WO ‘118 further does not anticipate the claims of the ‘560 patent because it does not  
20 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a  
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<sup>4073</sup> *Atofina*, 441 F.3d at 1000.

23 <sup>4074</sup> *Id.*

24 <sup>4075</sup> *Id.*



1 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.  
2 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high  
3 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and  
4 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or  
5 higher, and still more preferably 96.5% by weight or higher.”<sup>4076</sup> Therefore, WO ‘118 discloses  
6 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total  
7 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed  
8 generic range for the EPA composition in the claimed pharmaceutical composition.

9 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the  
10 . . . range claimed in the” patent is insufficient for anticipation.<sup>4077</sup> In *Atofina*, the prior art  
11 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a  
12 range between 330 and 450 degrees. The court explained that this slight overlap “is not  
13 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”<sup>4078</sup> and therefore failed  
14 to anticipate the claimed range.<sup>4079</sup> The court in *Atofina* also found that a prior art disclosure of a  
15 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0  
16 percent.<sup>4080</sup> The court explained that “although there is a slight overlap, no reasonable fact finder  
17 could determine that this overlap describes the entire claimed range with sufficient specificity to  
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21 <sup>4076</sup> WO ‘118 at 22.

22 <sup>4077</sup> *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

23 <sup>4078</sup> *Atofina*, 441 F.3d at 1000.

24 <sup>4079</sup> *Atofina*, 441 F.3d at 1000.

<sup>4080</sup> *Id.*

1 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no  
2 anticipation.”<sup>4081</sup>

3 Similarly, although there may be some overlap between the E-EPA content disclosed by  
4 WO ‘118 and the ranges claimed by the ‘560 patent, WO ‘118 does not specifically highlight the  
5 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a  
6 critical factor of the invention disclosed in the ‘560 patent. Therefore, WO ‘118’s broad  
7 disclosure of the E-EPA content in its invention does not describe the claimed range with  
8 sufficient specificity and cannot anticipate the independent claims of the ‘560 patent.

9 WO ‘118 is additionally insufficient for anticipation because it does not expressly  
10 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118  
11 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is  
12 DHA-E.”<sup>4082</sup> The disclosure goes on to state that the composition of the invention is preferably  
13 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed  
14 pharmaceutical composition is a critical factor of the invention disclosed in the ‘560 patent.

15 The disclosure of WO ‘118 treats DHA and EPA interchangeably. The disclosed  
16 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.  
17 There is no express teaching or guidance directing the person of ordinary skill in the art to the  
18 claimed EPA compositions, Therefore, WO ‘118’s broad disclosure, which indicates no  
19 difference between the use of EPA or DHA in its invention, cannot anticipate the independent  
20 claims of the ‘560 patent.

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23 <sup>4081</sup> *Id.*

24 <sup>4082</sup> WO ‘118 at 22.

1 Defendants contend that Plaintiffs are estopped from arguing there is any material  
2 difference between “not more than about 4% DHA” and “substantially no DHA.” Defendants  
3 provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing  
4 data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is  
5 without merit. Plaintiffs’ clinical data cannot form the basis for an estoppel argument and  
6 Defendants have cited no authority to support their position suggesting the contrary. The  
7 language of “not more than about 4% DHA” and “substantially no DHA” are different phrases  
8 and are not co-extensive. Accordingly, plaintiffs are not estopped.

9 In the same paragraph containing their allegation of estoppel, Defendants also quote from  
10 Amarin’s 2011 10-K. It is unclear whether these quotations are associated with their  
11 unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these  
12 statements form the basis for any theory of estoppel. To the extent that Defendants quote  
13 Amarin’s post-invention 10-K to make any invalidity argument, that is also unavailing. The  
14 quoted statements do not identify any recited claim element, including the specific  
15 pharmaceutical composition, the recited patient population, administration in the manner  
16 claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from  
17 the quoted statements.

18 (4) WO ‘118 Does Not Describe the Dependent Claims

19 Defendants fail to address any of the claim elements of the dependent claims.  
20 Defendants appear to concede that WO ‘118 does not expressly teach these elements, as they fail  
21 to set forth any meaningful basis for concluding that WO ‘118 teaches these elements.  
22 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by  
23 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to  
24 no patentable weight.” To the extent the recited claim elements relate to the administration step,

1 the dosage form or characteristics of the treated subject and the specific effect produced by the  
2 claimed method, Defendants’ contentions that the claim limitations are inherent properties of  
3 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO  
4 ‘118, they fail to identify any basis, explanation, or even supporting argument for that assertion.  
5 Defendants have not met the burden to establish anticipation with the naked assertion that the  
6 effects are inherent, natural properties of EPA.

7 Further, Defendants entirely fail to prove that inherently discloses the recited claim  
8 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot  
9 inherently anticipate as a matter of law.”<sup>4083</sup> “[A]nticipation by inherent disclosure is appropriate  
10 only when the reference discloses prior art that must *necessarily* include the unstated  
11 limitation.”<sup>4084</sup> “It is not sufficient if a material element or limitation is ‘merely probably or  
12 possibly present’ in the prior art.”<sup>4085</sup> Defendants fail to show that WO ‘118 “*necessarily*” meets  
13 the recited claim elements relating to the administration step, the dosage form or characteristics  
14 of the treated subject and the specific effect produced by the claimed method *every time*. WO  
15 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total  
16 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in  
17 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,  
18 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and  
19 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim  
20 elements.

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22 <sup>4083</sup> *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 <sup>4084</sup> *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 <sup>4085</sup> *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).



1 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,  
2 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori  
2000 and/or Maki.”

- 3 • 3) “. . .the asserted claims of the ’560 patent would have been obvious over the  
4 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of  
5 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view  
6 of Satoh or Shinozaki in further view of Contacos.”
- 7 • 4) “. . . the asserted claims of the ’560 patent would have been obvious over WO ’118  
8 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the  
9 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 10 • 5) “. . . the asserted claims of the ’560 patent would have been obvious over WO  
11 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment  
12 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and  
13 further in view of Katayama, Matsuzawa and/or Takaku.”

14 A patent claim is invalid “if the differences between the subject matter sought to be  
15 patented and the prior art are such that the subject matter as a whole would have been obvious at  
16 the time the invention was made to a person having ordinary skill in the art.”<sup>4089</sup> Obviousness is  
17 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,  
18 (2) the scope and content of the prior art, and (3) the differences between the prior art and the  
19 claims at issue.<sup>4090</sup>

20 In evaluating obviousness, each prior art reference must be evaluated for all that it  
21 teaches, including the portions that would lead away from the claimed invention.<sup>4091</sup> Indeed, any  
22 teaching in the art that points away from the claimed invention must be considered.<sup>4092</sup> A  
23 reference teaches away if a person of ordinary skill, upon reading the reference, would be  
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21 <sup>4089</sup> 35 U.S.C. § 103(a).

22 <sup>4090</sup> *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

23 <sup>4091</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 <sup>4092</sup> *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

1 discouraged from following the path set out in the reference, or would be led in a direction  
2 divergent from the path that was taken by the applicant.<sup>4093</sup> For instance, a reference teaches  
3 away if it suggests that the line of development flowing from the reference's disclosure is  
4 unlikely to be productive of the result sought by the applicant.<sup>4094</sup>

5 In order to find obviousness based on a combination of references, there must be some  
6 rationale for combining the references in the way claimed that is separate and apart from the  
7 hindsight provided by the patented invention itself.<sup>4095</sup> The law prohibits an obviousness  
8 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art  
9 references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of  
10 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed  
11 invention."<sup>4096</sup> "The invention must be viewed not after the blueprint has been drawn by the  
12 inventor, but as it would have been perceived in the state of the art that existed at the time the  
13 invention was made."<sup>4097</sup>

14 "The determination of obviousness is made with respect to the subject matter as a whole,  
15 not separate pieces of the claim."<sup>4098</sup> "[A] patent composed of several elements is not proved  
16 obvious merely by demonstrating that each of its elements was, independently, known in the  
17 prior art."<sup>4099</sup> "This is so because inventions in most, if not all, instances rely upon building

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19 <sup>4093</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

20 <sup>4094</sup> *Id.*

21 <sup>4095</sup> *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

22 <sup>4096</sup> *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

23 <sup>4097</sup> *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

24 <sup>4098</sup> *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

<sup>4099</sup> *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

1 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations  
2 of what, in some sense, is already known.”<sup>4100</sup>

3 Accordingly, it is improper to pick and choose isolated elements from the prior art and  
4 combine them so as to yield the invention<sup>4101</sup> or to modify a prior art reference in a way that  
5 “would destroy the fundamental characteristics of that reference.”<sup>4102</sup> Moreover, a combination  
6 is not obvious where “it would be impossible to apply these teachings [of the secondary  
7 reference] to the [primary reference] without entirely changing the basic mechanism and  
8 procedure thereof,”<sup>4103</sup> or where the proposed combination requires “material and radical  
9 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the  
10 prior art device.<sup>4104</sup> Furthermore, it is improper “to modify the secondary reference before it is  
11 employed to modify the primary reference” in assessing obviousness.<sup>4105</sup>

12 Further, a party asserting obviousness in view of a combination of prior art disclosures  
13 must show that a person of ordinary skill in the relevant field had an “apparent reason” to  
14 combine the elements in the manner claimed<sup>4106</sup> and “a reasonable expectation of success.”<sup>4107</sup>

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16 <sup>4100</sup> *KSR*, 550 U.S. at 418-419.

17 <sup>4101</sup> *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

18 <sup>4102</sup> *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

19 <sup>4103</sup> *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

20 <sup>4104</sup> *Id.* at 88.

21 <sup>4105</sup> *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

22 <sup>4106</sup> *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may  
23 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*  
24 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*  
*Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

<sup>4107</sup> *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);  
*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a  
combination of elements “must do more than yield a predictable result;” combining elements that work together “in  
an unexpected and fruitful manner” would not have been obvious).



1 For chemical compounds, there must have been a reason both to select the prior art  
2 compound “most promising to modify” and to make the necessary changes to arrive at the  
3 claimed compound.<sup>4108</sup> This protects against the use of hindsight to pick through the prior art  
4 based solely on structural similarity to the claimed compound.<sup>4109</sup> Any assertion of an “apparent  
5 reason” must find a basis in the factual record.<sup>4110</sup>

6 The “reasonable expectation of success” for a chemical compound must be of all of a  
7 claimed compound’s relevant properties,<sup>4111</sup> including those discovered after the patent was filed  
8 or even issued.<sup>4112</sup> “The basic principle behind this rule is straight-forward—that which would  
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10 <sup>4108</sup> *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–  
11 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli  
Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

12 <sup>4109</sup> *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at \*14. *Accord In re Vaidyanathan*, 381. 985, 994  
13 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.  
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.  
2002).

14 <sup>4110</sup> *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions  
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to  
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the  
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at  
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the  
invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed  
19 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438  
F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in  
light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that  
20 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
21 motivated to resolve citalopram in June 1988”).

22 <sup>4111</sup> *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success  
23 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .  
24 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of  
pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d  
820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . . Here, the  
ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of  
pharmacological properties that it possesses.”).

<sup>4112</sup> *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at  
908.

1 have been surprising to a person of ordinary skill in a particular art would not have been  
2 obvious.”<sup>4113</sup> Any assertion of a “reasonable expectation of success” must find a basis in the  
3 factual record.<sup>4114</sup>

4 In an obviousness determination, any objective indicia of nonobviousness must be taken  
5 into account.<sup>4115</sup> An objective indicium is any “event[] proved to have actually happened in the  
6 real world” that evidences the nonobvious nature of the invention.<sup>4116</sup> The existence of an  
7 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or  
8 surprising results, expressions of skepticism, industry praise, commercial success, and copying  
9 are classical indicia of nonobviousness.<sup>4117</sup> These factual inquiries “guard against slipping into  
10 use of hindsight,”<sup>4118</sup> and “may often be the most probative and cogent evidence of  
11 nonobviousness.”<sup>4119</sup>

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14 <sup>4113</sup> *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.”).

15 <sup>4114</sup> See, e.g., *Sanofi-Synthelabo*, 550 F.3d at 1089 (“Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was ‘particularly expected’ that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant ‘established a substantial record of unpredictability vis-à-vis a highly significant combination of properties.’”).

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19 <sup>4115</sup> *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

20 <sup>4116</sup> *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

21 <sup>4117</sup> *Graham*, 383 U.S. at 17–18; KSR, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

22 <sup>4118</sup> *Graham*, 383 U.S. at 36.

23 <sup>4119</sup> *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting Inc. v. Lampros Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

1 Also, as with assertions of anticipation, in order for an invention to be obvious, it must  
2 have been fully “in possession” of the public—which requires that the claimed invention have  
3 been enabled.<sup>4120</sup>

4 A element-by-element analysis, identifying each limitation of each asserted claim that is  
5 absent from the prior art, is provided below, and also provided at Exhibit I. The contentions  
6 below are incorporated by reference into Exhibit I, and vice-versa.

7 a) General Overview

8 Defendants fail to provide a single prior art reference that discloses administration of the  
9 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population  
10 ( $\geq 500$  mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,  
11 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying  
12 degrees of purity, in a wide range of doses and administration periods, to subjects who have  
13 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance  
14 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo  
15 controlled studies are considered the “gold standard” of clinical studies. Studies involving the  
16 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot  
17 distinguish between the effect of the placebo from that of the active agent. Studies which  
18 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the  
19 independent effects of EPA and DHA.<sup>4121</sup> Inconsistency in dosages and administration periods

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21 <sup>4120</sup> *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for  
22 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,  
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for  
23 making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound  
24 itself is in the possession of the public.”).

<sup>4121</sup> *Mori* 2006 at 96.

1 and variations in the administered fatty acid compositions also complicate the interpretation of  
2 the results and limit the application of these studies.

3 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with  
4 very high TGs together with patients with high and borderline high TGs indicates that there is no  
5 medical difference in responsiveness to treatment among the groups of people.”<sup>4122</sup> Defendants  
6 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-  
7 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in  
8 patients with high triglycerides ( $\geq 200$  mg/dL and  $< 500$  mg/dL) who were also on statin therapy.  
9 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g  
10 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG  
11 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that  
12 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.<sup>4123</sup> In  
13 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were  
14 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use  
15 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a  
16 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the  
17 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to  
18 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.  
19 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical  
20 difference in responsiveness to treatment between the very-high TG patient population and lower

21 \_\_\_\_\_  
22 <sup>4122</sup> Defendants’ Joint Invalidity Contentions at 579 (*see* FN 106).

23 <sup>4123</sup> FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6  
24 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been  
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline  
TG values < 500 mg/dL).

1 TG patient populations merely because there was possibly one patient with baseline TG levels of  
2 at least 500 mg/dL.

3 As discussed above in Section III, patients with very-high TG levels were considered  
4 fundamentally different from patients with borderline-high or high TGs from a clinical,  
5 regulatory, and therapeutic perspective.<sup>4124</sup> Clinically, the authoritative guidance to physicians  
6 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III  
7 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;  
8 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients  
9 was atherosclerosis, while the primary risk faced by very-high TG patients was acute  
10 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for  
11 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for  
12 very-high TG patients was TG reduction. This distinction between patients with borderline-  
13 high/high TG levels and patients with very high TG levels is also observed on the regulatory  
14 level. The FDA recognized the different clinical status of the very-high TG population by  
15 approving some drugs specifically for the very-high TG group without granting treatment  
16 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).<sup>4125</sup>

17 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the  
18 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the  
19 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known  
20 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the  
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23 \_\_\_\_\_  
<sup>4124</sup> See Bays Jan. 8, 2012 Decl., ¶ 20.

24 <sup>4125</sup> See Bays Jan. 8, 2012 Decl., ¶ 22.

1 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG  
2 level of the patient receiving treatment.

3 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but  
4 increase LDL-C in very-high TG patients.<sup>4126</sup> The fibrate, Tricor (fenofibrate), for example,  
5 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)<sup>4127</sup>  
6 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).<sup>4128</sup> In  
7 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-  
8 significant increase in LDL-C was observed.<sup>4129</sup> In patients with very-high TGs (mean baseline  
9 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).<sup>4130</sup> Similar  
10 results were seen with the administration of Lopid (gemfibrozil).<sup>4131</sup> The differing effects of  
11 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values  
12 demonstrates how a person of ordinary skill at the time of the invention would have understood  
13 that one could not simply assume that an observed effect of a TG-lowering agent on lipid  
14 parameters in patients with normal, borderline-high or high TG levels would be the same in  
15 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or  
16 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with  
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18 <sup>4126</sup> See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain  
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

19 <sup>4127</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

20 <sup>4128</sup> *Id.*

21 <sup>4129</sup> *Id.* See also, Trilipix Label at 27.

22 <sup>4130</sup> *Id.* See also, Trilipix Label at 27.

23 <sup>4131</sup> See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels  
had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was  
dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while  
subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

1 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-  
 2 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean  
 3 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level  
 4 of 726 mg/dL) experience significantly increased LDL-C levels.

<b>Fibrate</b>	<b>Mean Baseline TG Value</b>	<b>TG</b>	<b>LDL-C</b>	<b>HDL-C</b>	<b>Total-C</b>
Tricor (fenofibrate) <sup>4132</sup>	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

\* = p < 0.05 vs. Placebo

11 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing  
 12 lipid effects depending on the patient's baseline TG level. When administered to patients with  
 13 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-  
 14 C.<sup>4133</sup> It had no significant effect on other lipid-related variable, including LDL-C and Apo-  
 15 B.<sup>4134</sup> However, when administered to patients with very-high baseline TG levels, TGs were  
 16 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.<sup>4135</sup>  
 17 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of  
 18 Lovaza/Omacor was beneficial.<sup>4136</sup>

<sup>4132</sup> Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

<sup>4133</sup> Chan 2002 I at 2379-81.

<sup>4134</sup> *Id.*; See also, Westphal at 918.

<sup>4135</sup> See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

<sup>4136</sup> See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) ("Treatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to

1 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply  
2 assume that a lipid lowering agent would have the same effect in a patient with very-high TG  
3 levels ( $\geq 500$  mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They  
4 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when  
5 the normal, borderline-high or high TG patient populations were administered omega-3 fatty  
6 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was  
7 expected as a natural consequence of lowering TGs. A person of ordinary skill would have  
8 considered the rise in LDL-C to be a direct consequence of TG lowering through increased  
9 VLDL particle conversion.<sup>4137</sup> Because normal to high TG patients did not have the large  
10 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not  
11 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree  
12 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,  
13 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the

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15 one that may be less atherogenic by changing LDL structure; lowering serum [cholesteryl ester transfer activity],  
16 serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely  
17 raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic  
18 light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was  
19 substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not  
20 be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe  
21 hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the  
22 long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm  
23 or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular  
24 risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty  
acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C  
levels (TC minus HDL-C.)”

21 <sup>4137</sup> Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class  
22 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels  
23 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during  
24 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some  
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the  
decrease in VLDL.”).



1 highest baseline TG levels<sup>4138</sup> and did not increase for patients with lower TG levels. Therefore,  
2 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,  
3 borderline-high or high TG patients was *expected*.

4 Defendants contend that “a composition and its properties are inseparable, and therefore  
5 do not impart any additional patentability,” and that “all of the limitations regarding the  
6 properties of the ethyl EPA compound identified in the claims of the ‘560 patent are inherent to  
7 the compound when administered to a human subject.”<sup>4139</sup> Inherency may not supply a missing  
8 claim limitation in an obviousness analysis unless the inherency would have been obvious to one  
9 of ordinary skill in the art.<sup>4140</sup> Obviousness is based on what is *known* in the art at the time of the  
10 invention.<sup>4141</sup> It was not known or reasonably expected at the time of the claimed invention that  
11 purified EPA, when administered to patients with very-high TG levels ( $\geq 500$  mg/dL), would not  
12 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and  
13 Apo-B necessarily present, or the natural result of the combination of elements explicitly  
14 disclosed by the prior art.<sup>4142</sup> Therefore, inherency does not supply the missing claim elements  
15 in the prior art cited by Defendants.

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18 <sup>4138</sup> Bays 2008 I at 400-402.

19 <sup>4139</sup> Defendants’ Joint Invalidity Contentions at 579-80.

20 <sup>4140</sup> See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .  
21 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an  
22 obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of  
23 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere  
24 fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

<sup>4141</sup> *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.  
Obviousness cannot be predicated on what is unknown.”).

<sup>4142</sup> See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

1 Defendants argue that the claims of the ‘560 patent which contain “a limiting clause, such  
2 as ‘effects,’ ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step  
3 positively recited and therefore are not elements.<sup>4143</sup> This is incorrect. “There is nothing  
4 inherently wrong with defining some part of an invention in functional terms.”<sup>4144</sup> When a  
5 clause “states a condition that is material to patentability, it cannot be ignored in order to change  
6 the substance of the invention.”<sup>4145</sup> The claim term “to effect” acts as a positive limitation if the  
7 term represents “unexpected and improved effects of administration of the claimed  
8 compound.”<sup>4146</sup> In addition, the elements represent unexpected and improved effects of  
9 administration of purified EPA, because a person of ordinary skill would not have expected no  
10 substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe  
11 hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and  
12 reduction in Apo-B must be accorded patentable weight.

13 b) Identification of Claim Elements Absent from Each Item of Prior  
14 Art

15 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.  
16 Where a limitation is absent from any Independent Claim, that limitation is absent from all  
17 asserted claims, and that analysis is incorporated by reference into each dependent claim. For  
18 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted  
19 claims is not a concession that such limitation is present in the reference. By discussing  
20

21 <sup>4143</sup> Defendants’ Joint Invalidity Contentions at 580.

22 <sup>4144</sup> See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

23 <sup>4145</sup> *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

24 <sup>4146</sup> *AstraZeneca AB v. Dr. Reddy’s Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at \*11–12 (D.N.J. May 18, 2010).

1 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants  
2 have appropriately divided the claim language for any purpose.

3 (1) WO '118

4 WO '118 discloses a composition containing EPA-E for preventing the occurrence of  
5 cardiovascular events in multiple risk patients.

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
7 '118 disclose or suggest elements of the '560 Claims. The cited portions of WO '118 do not  
8 disclose or suggest these elements at least because they do not disclose or suggest administration  
9 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
10 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition  
11 with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not  
12 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed  
13 TG level.

14 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
15 WO '118 does not disclose or suggest a subject with the recited very high TG level. WO '118  
16 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
17 acid composition or dosage. WO '118 further does not disclose or suggest a method to effect the  
18 recited TG reduction in the subject with the claimed TG level. With respect to claim 11, WO  
19 '118 does not disclose or suggest a method to effect a reduction in TG in the subject based on a  
20 comparison to placebo control.

21 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
22 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this  
23 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
24 claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the

1 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
2 Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
3 the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference  
4 fails to disclose or suggest the recited capsule dosage.

5 (2) WO '900

6 WO '900 describes methods for obtaining EPA-rich compositions.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO  
8 '900 disclose or suggest elements of the '560 Claims. The cited portions of WO '900 do not  
9 disclose or suggest these elements at least because they do not disclose or suggest administration  
10 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
11 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition  
12 with the recited fatty acid dosage or administration period. The cited portions of WO '900  
13 further do not disclose or suggest a method to effect the recited TG reduction in the subject with  
14 the claimed TG level.

15 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
16 WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900  
17 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
18 acid dosage or administration period. WO '900 further does not disclose or suggest a method to  
19 effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim  
20 11, WO '900 does not disclose or suggest the recited effect based on a comparison to a placebo  
21 control.

22 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
23 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this  
24 reference fails to disclose or suggest the subject having the recited baseline lipid levels. With

1 respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and  
2 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this  
3 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with  
4 the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest  
5 the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to  
6 Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

7 (3) Contacos

8 Contacos describes a study designed to determine the safety and efficacy of a statin  
9 (pravastatin) combined with fish oil either alone or in combination, for the management of  
10 patients with mixed hyperlipidemia.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
12 Contacos disclose or suggest elements of the '560 Claims. The cited portions of Contacos do not  
13 disclose or suggest these elements at least because they do not disclose or suggest administration  
14 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
15 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition  
16 with the recited fatty acid compositions, dosage, or administration period. The cited portions of  
17 Contacos further do not disclose or suggest a method of administering the claimed  
18 pharmaceutical composition to effect to effect the recited TG reduction in the subject with the  
19 claimed TG level.

20 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
21 Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos  
22 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
23 acid compositions, dosage, or administration period. Contacos further does not disclose or  
24 suggest a method of administering the claimed pharmaceutical composition to effect to effect the

1 recited TG reduction in the subject with the claimed TG level. With respect to Claim 11,  
2 Contacos does not disclose or suggest a method of administering the claimed pharmaceutical  
3 composition to effect the recited TG reduction based on a comparison to a placebo control.

4 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
5 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
6 C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
7 administration of the claimed pharmaceutical composition to effect the recited reduction in  
8 Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the  
9 administration of the claimed pharmaceutical composition to effect the recited reduction in  
10 VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the  
11 recited capsule dosage.

12 (4) Grimsgaard

13 Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design  
14 intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids,  
15 apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG  
16 levels.

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
18 Grimsgaard disclose or suggest elements of the '560 Claims. The cited portions of Grimsgaard  
19 do not disclose or suggest these elements at least because they do not disclose or suggest  
20 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
21 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical  
22 composition with the recited administration period. The cited portions of Grimsgaard further do  
23 not disclose or suggest a method to effect the recited TG reduction in the subject with the  
24 claimed TG level.

1 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
2 Grimsgaard does not disclose or suggest a subject with the recited very high TG level.  
3 Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the  
4 recited administration period. Grimsgaard further does not disclose or suggest a method to effect  
5 the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11,  
6 Grimsgaard does not disclose or suggest a method to effect a reduction in TG in the subject with  
7 the claimed TG levels based on a comparison to placebo control.

8 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
9 the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to  
10 Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in  
11 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this  
12 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the  
13 claimed TG level. With respect to Claims 8-9 and 18-19, this reference fails to disclose or  
14 suggest the recited capsule dosage.

15 (5) Hayashi

16 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for  
17 8 weeks. The purity of the composition is not reported. The study was not placebo controlled  
18 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride  
19 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220  
20 mg/dl.

21 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the  
22 '560 patent claims. For example, the cited portions of Hayashi do not disclose or suggest  
23 administration of EPA with the recited purity to a subject with the recited very high TG levels  
24 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject

1 had a TG level above 400 mg/dl. The cited portions of Hayashi further do not disclose or  
2 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or  
3 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the  
4 recited TG reduction without substantially increasing LDL-C in a subject with the recited very  
5 high TG levels.

6 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
7 Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also  
8 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or dosage. Hayashi further does not disclose or suggest a method to effect the  
10 recited TG reduction in the subject with the claimed TG level. With respect to Claim 11,  
11 Hayashi does not disclose or suggest the recited effect based on a comparison to a placebo  
12 control.

13 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
14 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this  
15 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
16 claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
17 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
18 Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
19 the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference  
20 fails to disclose or suggest the recited capsule dosage.

21 (6) Katayama

22 Katayama was directed to an investigation of the safety and efficacy of Epedel during  
23 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,  
24



1 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and  
2 was not placebo controlled.

3 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
4 Katayama disclose or suggest elements of the '560 Claims. The cited portions of Katayama do  
5 not disclose or suggest these elements at least because they do not disclose or suggest  
6 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
7 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical  
8 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama  
9 further do not disclose or suggest a method to effect the recited TG reduction in the subject with  
10 the claimed TG level.

11 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
12 Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama  
13 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
14 acid compositions or dosage. Katayama further does not disclose or suggest a method to effect  
15 the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11,  
16 Katayama does not disclose or suggest the recited effect based on a comparison to a placebo  
17 control.

18 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
19 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this  
20 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
21 claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
22 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
23 Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
24

1 the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference  
2 fails to disclose or suggest the recited capsule dosage.

3 (7) Leigh-Firbank

4 Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle  
5 density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank  
6 does not administer EPA of the purity recited in the claims.

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
8 Leigh-Firbank disclose or suggest elements of the '560 Claims. The cited portions of Leigh-  
9 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest  
10 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
11 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed  
12 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration  
13 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method  
14 administering the claimed pharmaceutical composition to effect the recited TG reduction in the  
15 subject with the claimed TG level.

16 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
17 Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-  
18 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the  
19 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not  
20 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
21 the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11,  
22 Leigh-Firbank does not disclose or suggest a method of administering the claimed  
23 pharmaceutical composition to effect the recited TG reduction based on a comparison to a  
24 placebo control.

1 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
2 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
3 C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
4 administration of the claimed pharmaceutical composition to effect the recited reduction in  
5 Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the  
6 administration of the claimed pharmaceutical composition to effect the recited reduction in  
7 VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the  
8 recited capsule dosage.

9 (8) Lovaza PDR

10 The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
12 Lovaza PDR disclose or suggest elements of the '560 Claims. The cited portions of the Lovaza  
13 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
14 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
15 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed  
16 pharmaceutical composition with the recited fatty acid compositions or administration period.  
17 The cited portions of the Lovaza PDR further do not disclose or suggest a method administering  
18 the claimed pharmaceutical composition to effect the recited TG reduction.

19 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), the  
20 Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the  
21 recited fatty acid compositions, dosage, or administration period. The Lovaza PDR further does  
22 not disclose or suggest a method of administering the claimed pharmaceutical composition to  
23 effect the recited TG reduction. With respect to Claim 11, the Lovaza PDR does not disclose or  
24

1 suggest a method of administering the claimed pharmaceutical composition to effect the recited  
2 TG reduction based on a comparison to a placebo control.

3 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
4 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
5 C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
6 administration of the claimed pharmaceutical composition to effect the recited reduction in  
7 Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the  
8 administration of the claimed pharmaceutical composition to effect the recited reduction in  
9 VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the  
10 recited capsule dosage.

11 (9) Maki

12 Maki administered 1.52g/day DHA supplements to patients with below-average levels of  
13 HDL-C. Maki does not administer EPA of the purity recited in the claims.

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki  
15 disclose or suggest elements of the '560 Claims. The cited portions of Maki do not disclose or  
16 suggest these elements at least because they do not disclose or suggest administration of EPA  
17 with the recited purity to a subject with the recited very high TG levels. The cited portions of  
18 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited  
19 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do  
20 not disclose or suggest a method of administering the claimed pharmaceutical composition to  
21 effect the recited TG reduction in the subject with the claimed TG level.

22 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
23 Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does  
24 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

1 compositions, dosage, or administration period. Maki further does not disclose or suggest a  
2 method of administering the claimed pharmaceutical composition to effect the recited TG  
3 reduction in the subject with the claimed TG level. With respect to Claim 11, Maki does not  
4 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
5 the recited TG reduction based on a comparison to a placebo control.

6 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
7 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
8 C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
9 administration of the claimed pharmaceutical composition to effect the recited reduction in  
10 Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the  
11 administration of the claimed pharmaceutical composition to effect the recited reduction in  
12 VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the  
13 recited capsule dosage.

14 (10) Matsuzawa

15 Matsuzawa administered Epadel to patients with hyperlipaemia in order to study its long-  
16 term use in the treatment of the disease and was not placebo controlled.

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
18 Matsuzawa disclose or suggest elements of the '560 Claims. The cited portions of Matsuzawa  
19 do not disclose or suggest these elements at least because they do not disclose or suggest  
20 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
21 The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical  
22 composition with the recited fatty acid compositions or dosage. The cited portions of  
23 Matsuzawa further do not disclose or suggest a method of administering the claimed  
24

1 pharmaceutical composition to effect to effect the recited TG reduction in the subject with the  
2 claimed TG level.

3 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
4 Matsuzawa does not disclose or suggest a subject with the recited very high TG level.  
5 Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the  
6 recited fatty acid compositions or dosage. Matsuzawa further does not disclose or suggest a  
7 method of administering the claimed pharmaceutical composition to effect to effect the recited  
8 TG reduction in the subject with the claimed TG level. With respect to Claim 11, Matsuzawa  
9 does not disclose or suggest the recited effect based on a comparison to a placebo control.

10 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
11 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
12 C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this  
13 reference fails to disclose or suggest the administration of the claimed pharmaceutical  
14 composition to effect the recited reduction in Apolipoprotein B in the subject with the claimed  
15 TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the  
16 administration of the claimed pharmaceutical composition to effect the recited reduction in  
17 VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this  
18 reference fails to disclose or suggest the recited capsule dosage.

19 (11) Mori 2000

20 Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum  
21 lipids and lipoproteins, glucose and insulin in humans.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
23 2000 disclose or suggest elements of the '560 Claims. The cited portions of Mori 2000 do not  
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
2 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition  
3 with the recited dosage or administration period. The cited portions of Mori 2000 further do not  
4 disclose or suggest a method to effect the recited TG reduction in the subject with the claimed  
5 TG level.

6 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
7 Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000  
8 also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage  
9 or administration period. Mori 2000 further does not disclose or suggest a method to effect the  
10 recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Mori  
11 2000 does not disclose or suggest a method to effect a reduction in TG in the subject with the  
12 claimed TG levels based on a comparison to placebo control.

13 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
14 the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to  
15 Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in  
16 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this  
17 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the  
18 claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or  
19 suggest the recited capsule dosage.

20 (12) Mori 2006

21 Mori 2006 is a review which reports data from clinical trials which compared the  
22 independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

23 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori  
24 2006 disclose or suggest elements of the '560 Claims. The cited portions of Mori 2006 do not

1 disclose or suggest these elements at least because they do not disclose or suggest administration  
2 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
3 portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition  
4 with the recited fatty acid dosage or administration period. The cited portions of Mori 2006  
5 further do not disclose or suggest a method to effect the recited TG reduction in the subject with  
6 the claimed TG level.

7 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
8 Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006  
9 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty  
10 acid dosage or administration period. Mori 2006 further does not disclose or suggest a method to  
11 effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim  
12 11, Mori 2006 does not disclose or suggest the recited effect based on a comparison to a placebo  
13 control.

14 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest  
15 the subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this  
16 reference fails to disclose or suggest the subject having the recited baseline lipid levels. With  
17 respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and  
18 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this  
19 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with  
20 the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest  
21 the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to  
22 Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.



1 (13) Nozaki

2 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The  
3 purity of the composition is reported as 90%. The study was not placebo controlled and was  
4 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165  
5 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG  
6 patient population.

7 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the  
8 ‘560 patent claims. For example, the cited portions of Nozaki do not disclose or suggest  
9 administration of EPA with the recited purity to a subject with the recited very high TG levels  
10 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do  
11 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
12 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a  
13 method to effect the recited TG reduction without substantially increasing LDL-C in a subject  
14 with the recited very high TG levels.

15 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the  
16 ‘560 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least  
17 because they do not disclose or suggest administration of EPA with the recited purity to a subject  
18 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The  
19 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical  
20 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki  
21 further do not disclose or suggest a method to effect the recited TG reduction without  
22 substantially increasing LDL-C.

23 With respect to Claims 1 and 11 of the ‘560 Patent (and therefore all asserted claims),  
24 Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also

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1 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
2 compositions or dosage. Nozaki further does not disclose or suggest a method to effect the  
3 recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Nozaki  
4 does not disclose or suggest the recited effect based on a comparison to a placebo control.

5 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
6 subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this  
7 reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the  
8 claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
9 recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to  
10 Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in  
11 the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference  
12 fails to disclose or suggest the recited capsule dosage.

13 (14) Omacor PDR

14 The Omacor PDR is the Physicians' Desk Reference describing Omacor.

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the  
16 Omacor PDR disclose or suggest elements of the '560 Claims. The cited portions of the Omacor  
17 PDR do not disclose or suggest these elements at least because they do not disclose or suggest  
18 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
19 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed  
20 pharmaceutical composition with the recited fatty acid compositions or administration period.  
21 The cited portions of the Omacor PDR further do not disclose or suggest a method administering  
22 the claimed pharmaceutical composition to effect the recited TG reduction.

23 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), the  
24 Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the

1 recited fatty acid compositions, dosage, or administration period. The Omacor PDR further does  
2 not disclose or suggest a method of administering the claimed pharmaceutical composition to  
3 effect the recited TG reduction. With respect to Claim 11, the Omacor PDR does not disclose or  
4 suggest a method of administering the claimed pharmaceutical composition to effect the recited  
5 TG reduction based on a comparison to a placebo control.

6 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
7 the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-  
8 C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the  
9 administration of the claimed pharmaceutical composition to effect the recited reduction in  
10 Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the  
11 administration of the claimed pharmaceutical composition to effect the recited reduction in  
12 VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the  
13 recited capsule dosage.

14 (15) Satoh

15 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of  
16 PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects  
17 systemic inflammation.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
19 Satoh disclose or suggest elements of the '560 Claims. The cited portions of Satoh do not  
20 disclose or suggest these elements at least because they do not disclose or suggest administration  
21 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
22 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with  
23 the recited dosage or administration period. The cited portions of Satoh further do not disclose  
24 or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

1 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
2 Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does  
3 not disclose or suggest the claimed pharmaceutical composition with the recited dosage or  
4 administration period. Satoh further does not disclose or suggest a method to effect the recited  
5 TG reduction in the subject with the claimed TG level. With respect to Claim 11, Satoh does not  
6 disclose or suggest a method to effect a reduction in TG in the subject with the claimed TG  
7 levels based on a comparison to placebo control.

8 Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest  
9 the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to  
10 Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in  
11 Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this  
12 reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the  
13 claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or  
14 suggest the recited capsule dosage.

15 (16) Shinozaki

16 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and  
17 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
19 Shinozaki disclose or suggest elements of the '560 Claims. The cited portions of Shinozaki do  
20 not disclose or suggest these elements at least because they do not disclose or suggest  
21 administration of EPA with the recited purity to a subject with the recited very high TG levels.  
22 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical  
23 composition with the recited dosage or administration period. The cited portions of Shinozaki  
24

1 further do not disclose or suggest a method to effect the recited TG reduction in the subject with  
2 the claimed TG level.

3 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
4 Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki  
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage  
6 or administration period. Shinozaki further does not disclose or suggest a method to effect the  
7 recited TG reduction in the subject with the claimed TG level. With respect to Claim 11,  
8 Shinozaki does not disclose or suggest a method to effect a reduction in TG in the subject with  
9 the claimed TG levels based on a comparison to placebo control.

10 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
11 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this  
12 reference fails to disclose or suggest the subject having the recited baseline lipid levels. With  
13 respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and  
14 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this  
15 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with  
16 the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest  
17 the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to  
18 Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

19 (17) Takaku

20 Takaku administered Epadel to patients with hyperlipaemia in order to study its long-  
21 term use and was not placebo controlled.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of  
23 Takaku disclose or suggest elements of the '560 Claims. The cited portions of Takaku do not  
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG levels. The cited  
2 portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition  
3 with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not  
4 disclose or suggest a method of administering the claimed pharmaceutical composition to effect  
5 to effect the recited TG reduction in the subject with the claimed TG level.

6 With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims),  
7 Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also  
8 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid  
9 compositions or dosage. Takaku further does not disclose or suggest a method of administering  
10 the claimed pharmaceutical composition to effect to effect the recited TG reduction in the subject  
11 with the claimed TG level. With respect to Claim 11, Takaku does not disclose or suggest the  
12 recited effect based on a comparison to a placebo control.

13 Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the  
14 subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this  
15 reference fails to disclose or suggest the subject having the recited baseline lipid levels. With  
16 respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and  
17 LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this  
18 reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with  
19 the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest  
20 the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to  
21 Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

22 c) The Prior Art Does Not Render the Claims Obvious

23 Defendants have not identified by clear and convincing evidence that the asserted claims  
24 of the '560 patent would have been *prima facie* obvious in light of the references cited, either

1 alone or in combination. As described above, none of the references discloses all of the elements  
2 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without  
3 explanation, and argue they somehow must be combined to render obvious the asserted claims.  
4 Where Defendants have failed to make disclosures with the specificity required by Local Patent  
5 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the  
6 claim elements at issue.

7 Defendants' contentions fail to disclose each and every element of the claims of the '560  
8 patent. Specifically, Defendants do not contend that the relied upon references disclose the  
9 following element of Claim 11 (and therefore its dependent claims as well): administering the  
10 claimed pharmaceutical composition to the recited subject to effect a reduction in triglycerides  
11 based on a comparison to placebo control. Therefore, Defendants' prior art combinations cannot  
12 render the claims *prima facie* obvious.

13 Facts supporting the non-obviousness of the claims of the '560 patent are discussed in  
14 detail below. The objective indicia discussed in Section V.O further demonstrate that the '560  
15 patent is not obvious. In short, Defendants have not met their burden of showing that the claims  
16 would have been obvious.

- 17 (1) Defendants Do Not Demonstrate that the Independent  
18 Claims of the '560 patent Would Have Been Obvious
- 19 (a) Defendants Do Not Demonstrate that a Person of  
20 Ordinary Skill in the Art Would Have Had Any  
Reason to Replace the Mixed Fish Oil Active  
Ingredient in Lovaza with Pure EPA
- 21 (i) The '560 Patent is not Obvious Over the  
22 Omacor PDR/Lovaza PDR, in Combination  
with Katayama and/or Matsuzawa, Further  
23 in View of Nozaki and/or Hayashi and  
24

1  
2  
3 With respect to the '560 patent, Defendants present a combination of seven references:  
4 “the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering  
5 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or  
6 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000.”<sup>4147</sup> Defendants also present  
7 charts purporting to assert that an additional 61 references may be combined in order to render  
8 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary  
9 skill would combine 61 separate references, they additionally do not identify any motivation for  
10 combining these references.<sup>4148, 4149</sup> Although Defendants need not point to an explicit statement  
11 in the prior art motivating the combination of these references, any assertion of an “apparent  
12 reason” to combine must find a basis in the factual record.<sup>4150</sup> Defendants’ unsupported cobbling

13 <sup>4147</sup> Defendants’ Joint Invalidation Contentions at 574.

14 <sup>4148</sup> Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as  
15 described in the references cited above in Section V.B.2 in view of, at least, the references cited in V.B.3 and 4,  
16 including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matak, Maki,  
17 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,  
18 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2000,  
19 Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local  
20 Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidation  
21 Contentions at 573.

22 <sup>4149</sup> Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create  
23 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”  
24 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person  
having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references  
or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure  
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidation Contentions at 572.

<sup>4150</sup> *See, e.g., In re Vaidyanathan*, 381 F. App'x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the  
formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did  
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply  
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi  
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must  
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to  
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and



1 of selective disclosures represents hindsight reconstruction.<sup>4151</sup> Defendants’ contentions are no  
2 more than an assertion that certain claim elements were known in the prior art. Throughout their  
3 contentions, Defendants’ selectively cite to data points in a reference without considering other  
4 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all  
5 that it teaches.<sup>4152</sup> Accordingly, Defendants fail to meet their burden to establish *prima facie*  
6 obviousness.

7 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing  
8 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed  
9 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a  
10 method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the  
11 Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a  
12 significant increase in LDL-C levels in the very high TG patient population, for whom the  
13 product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,  
14 a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce  
15 TG levels in adult patients with very-high ( $\geq 500$  mg/dL) TG levels.

16 The proposed combinations do not render the independent claims of the ’560 patent  
17 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO  
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19 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.  
20 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*  
21 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding  
22 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been  
23 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

24 <sup>4151</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under  
*KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention  
without any explanation as to how or why the references would be combined to produce the claimed invention”).

<sup>4152</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza  
2 package insert specifically) during prosecution.<sup>4153</sup>

3 The analysis of the independent claims of the '560 patent is incorporated into all asserted  
4 claims that depend from those Claims.

5 (a) A Person of Ordinary Skill Would  
6 Not Have Been Motivated to  
7 Replace the Mixed Fish Oil Active  
8 Ingredient in Lovaza with Pure EPA

9 For an invention to be obvious, there must have been an “apparent reason” to make it.  
10 The subject matter of the '560 patent claims would not have been obvious in light of these  
11 references because a person of ordinary skill would not have been motivated to purify EPA or  
12 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
13 levels without an increase in LDL-C levels.

14 (i) Katayama and/or Matsuzawa  
15 Do Not Disclose Purported  
16 Known Clinical Benefits of  
17 Administering Pure EPA

18 Both Katayama and Matsuzawa are long term studies directed to an investigation of the  
19 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies  
20 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may  
21 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the  
22 art would not and could not attribute any observed effect (and the magnitude of that effect) to

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23 <sup>4153</sup> See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).

1 that of the drug. Any observed effect could be placebo dependent.<sup>4154</sup> As discussed above in  
2 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with  
3 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG  
4 patients because patients with higher TG levels had different lipid responses compared to  
5 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally  
6 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical  
7 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary  
8 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were  
9 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art  
10 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-  
11 high or high TG patients, was expected. At the priority date of the ‘560 patent, a person of  
12 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients  
13 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been  
14 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG  
15 lowering through increased VLDL particle conversion.

16 Defendants argue that these studies disclose known “clinical benefits” of administering  
17 pure EPA, lowering triglycerides without raising LDL-C.<sup>4155</sup> This is an incorrect characterization  
18 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of  
19 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.  
20 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.

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22 <sup>4154</sup>See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a  
23 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a  
24 placebo-controlled study and why results compared only to baseline may be misleading.)

<sup>4155</sup> Defendants’ Joint Invalidity Contentions at 575.

1 Defendants' selective citation of LDL-C data from these references represents the improper use  
2 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and  
3 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw  
4 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C  
5 levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the  
6 lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.<sup>4156</sup> The  
7 references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor  
8 would a person of ordinary skill view these references as teaching such a benefit for very-high  
9 TG patients.

10 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid  
11 effects. These studies fail to provide a head to head comparison of EPA versus DHA.  
12 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to  
13 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

14 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The  
15 purity of Epadel has varied over time and across different formulations of the product, therefore  
16 it is difficult to determine the purity of the version of Epadel used unless it is specified by the  
17 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the  
18 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and  
19 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference  
20 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

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<sup>4156</sup> Defendants' Joint Invalidation Contentions at 575.

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1 Nishikawa,<sup>4157</sup> published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.  
2 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite  
3 purity.<sup>4158</sup>

4 Further, Katayama and Matsuzawa were small studies conducted in only Japanese  
5 patients. These studies would not have been extrapolated to Western populations because the  
6 Japanese diet contains much more fish and has a number of other different attributes. The  
7 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In  
8 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where  
9 the patient population is exclusively Japanese cannot be generalized to other populations.<sup>4159</sup>  
10 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical  
11 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-  
12 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand  
13 that the Japanese respond differently to lipid lowering agents than Westerners.

14 Defendants rely on Katayama to demonstrate the "known clinical benefits of  
15 administering pure EPA - lowering triglycerides without raising LDL-C."<sup>4160</sup> However,  
16 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term  
17 treatment in patients with hyperlipidemia.<sup>4161</sup> Katayama does not disclose *any* LDL-C related  
18 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that

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20 <sup>4157</sup> Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS  
Analysis of PGI<sub>2</sub> and PGI<sub>3</sub> Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

21 <sup>4158</sup> See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

22 <sup>4159</sup> Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to  
other populations.").

23 <sup>4160</sup> Defendants' Joint Invalidity Contentions at 574 and 575.

24 <sup>4161</sup> Katayama at 2.

1 reference to provide any such disclosure. The only results disclosed by Katayama were a  
2 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was  
3 administered to patients with borderline-high to high TG levels, and its safety for long term use  
4 in this patient population.<sup>4162</sup> In addition to Katayama’s lack of disclosure regarding LDL-C,  
5 Defendants identify no other basis upon which a person of ordinary skill would have sought to  
6 combine the composition disclosed in Katayama with the Lovaza PDR.

7 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of  
8 administering pure EPA - lowering triglycerides without raising LDL-C.”<sup>4163</sup> However,  
9 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall  
10 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of  
11 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13  
12 were evaluated for improvement in serum triglycerides levels.<sup>4164</sup> It is unclear which of the 26  
13 patients were included in each separate evaluation; therefore one cannot determine the baseline  
14 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack  
15 of a placebo control makes it less likely that the results of this study can be generalized as an  
16 effect on any population as a whole and provides no insight with respect to the very-high TG  
17 patient population.

18 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,  
19 and one participant with TG levels > 1,000 mg/dL.<sup>4165</sup> However, when analyzing the lipid

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21 <sup>4162</sup> *Id.* at 16.

22 <sup>4163</sup> Defendants’ Joint Invalidation Contentions at 574.

23 <sup>4164</sup> Matsuzawa at 7 and 19.

24 <sup>4165</sup> *Id.* at 23.

1 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL  
2 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess  
3 triglyceride levels.”<sup>4166</sup> Fig. 4, which depicts the changes in serum triglycerides, shows that the  
4 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500  
5 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than  
6 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of  
7 undisclosed purity). The identification of three patients with TG levels between 400 and less  
8 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dL, and a person of  
9 ordinary skill would not understand that the reference makes any such disclosure. As discussed  
10 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG  
11 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no  
12 evidence to the contrary.

13 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a  
14 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.<sup>4167</sup> The disclosure  
15 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were  
16 excluded from the LDL-C results because the Friedewald’s Equation was used to calculate LDL-  
17 C levels. The Friedewald’s Equation cannot be used for patients with triglyceride levels of at  
18 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with  
19 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of  
20 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary  
21 skill in the art, however, would have expected the same treatment in patients with very high TG  
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23 <sup>4166</sup> *Id.* at 10.

24 <sup>4167</sup> *Id.* at 11.

1 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that  
2 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered  
3 triglyceride levels.<sup>4168</sup> At best, Matsuzawa demonstrates the uncertainty and confusion related to  
4 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify  
5 any other basis upon which a person of ordinary skill would have sought to combine the  
6 composition disclosed in Matsuzawa with the Lovaza PDR.

7 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that  
8 compositions comprising EPA as recited in the asserted claims lowers triglycerides without  
9 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA  
10 increases LDL-C.<sup>4169</sup> Defendants identify no other basis upon which a person of ordinary skill  
11 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank  
12 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the  
13 asserted claims of the '560 patent.

14 (ii) Nozaki and/or Hayashi  
15 Would Not Have Rendered  
16 the Asserted Claims Obvious

17 Defendants contend that the asserted claims of the '560 patent would have been obvious  
18 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
19 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted  
20 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
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22 <sup>4168</sup> *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA  
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific  
24 compositions used, or identify the patient populations were observed.

<sup>4169</sup> *See, e.g.,* Rambjor.



1 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
2 very high TG patient population.

3 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
4 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
5 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
6 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
7 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
8 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
9 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
10 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
11 patient population were abnormally high and would not have relied upon these results. Further,  
12 the person of skill in the art would not have looked to this patient population to predict the Apo-  
13 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
14 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
15 levels.<sup>4170</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
16 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
17 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
18 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
19 to the very high TG patient population.

20 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
21 the EPA and the DHA content in the composition that was administered is unknown. A person  
22 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28  
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24 <sup>4170</sup> Nozaki at 256.

1 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-  
2 C were not statistically significant.<sup>4171</sup> Further, the person of skill in the art would not have  
3 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very  
4 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success  
5 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA  
6 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,  
7 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is  
8 administered to the very high TG patient population.

9 Further, Hayashi was a small study conducted in only Japanese patients and was not  
10 placebo controlled. This study would not have been extrapolated to Western populations  
11 because the Japanese diet contains much more fish and has a number of other different attributes.  
12 The Japanese consume a higher amount of EPA and DHA in their diets than Western  
13 populations. In fact, Defendants' own reference states that the results from studies where the  
14 patient population is exclusively Japanese cannot be generalized to other populations.<sup>4172</sup> The  
15 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical  
16 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6  
17 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that  
18 the Japanese respond differently to lipid lowering agents than Westerners.

19 Further, Defendants have failed to offer a purported combination of references as part of  
20 their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any  
21 motivation to combine Nozaki and Hayashi with the other references of their purported  
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23 <sup>4171</sup> Hayashi at 26, Table I.

24 <sup>4172</sup> Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 obviousness combinations. Therefore, Defendants should be precluded from relying on these  
2 references.

3 (iii) Leigh-Firbank and/or Mori  
4 2000 Do Not Disclose  
5 Purported Knowledge that  
6 DHA was Responsible for the  
7 Increase in LDL-C

8 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that  
9 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-  
10 C levels.”<sup>4173</sup> Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*  
11 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants  
12 rely upon to support this statement does not categorize the increase in LDL-C as a “negative  
13 effect” in light of the overall impact of the disclosed composition on all lipid parameters.  
14 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As  
15 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C  
16 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—  
17 as in very-high TG patients because patients with higher TG levels had different lipid responses  
18 compared to patients with lower TG levels. Patients with very-high TG levels were considered  
19 fundamentally different from patients with borderline-high or high triglycerides from a lipid  
20 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person  
21 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)  
22 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but  
23 would substantially increase LDL-C in patients with very high TG levels.

24 <sup>4173</sup> Defendants’ Joint Invalidity Contentions at 577.

1 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was  
2 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,  
3 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride  
4 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either  
5 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A  
6 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any  
7 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the  
8 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)  
9 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated  
10 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA  
11 and DHA.<sup>4174</sup> A person of ordinary skill would understand that studies directed to EPA and  
12 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on  
13 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-  
14 Firbank, because purified EPA and DHA were not administered separately.

15 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent  
16 effects of EPA and DHA individually, even though it administered a combination of EPA and  
17 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions  
18 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet  
19 phospholipid EPA were *independently* associated with the decrease in fasting TGs,<sup>4175</sup> and DHA  
20 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state  
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23 <sup>4174</sup> Mori 2006 at 96.

24 <sup>4175</sup> Leigh-Firbank at 440.

1 of the art and numerous publications cited by Defendants.<sup>4176</sup> It is widely accepted that DHA  
2 also has a hypotriglyceridemic effect.

3 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients  
4 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-  
5 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching  
6 away from the claimed invention. “A reference may be said to teach away when a person of  
7 ordinary skill, upon [examining] the reference, would be discouraged from following the path set  
8 out in the reference, or would be led in a direction divergent from the path that was taken by the  
9 applicant.”<sup>4177</sup> Although teaching away is fact-dependent, “in general, a reference will teach  
10 away if it suggests that the line of development flowing from the reference’s disclosures is  
11 unlikely to be productive of the result sought by the applicant.”<sup>4178</sup>

12 Mori 2000 concludes that the changes effected by DHA supplementation “may represent  
13 a more favorable lipid profile than after EPA supplementation.”<sup>4179</sup> For example, it states that  
14 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL  
15 cholesterol and a significant increase in the HDL<sub>2</sub>-cholesterol subfraction, without adverse  
16 effects on fasting glucose concentrations.”<sup>4180</sup> Mori 2000 also states that “[d]espite an increase  
17 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may  
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20 <sup>4176</sup> See, e.g. Grimsgaard at 654.

21 <sup>4177</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

22 <sup>4178</sup> *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354  
(Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)  
23 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

24 <sup>4179</sup> Mori 2000 at 1092.

<sup>4180</sup> Mori 2000 at 1088.

1 be favorable.”<sup>4181</sup> Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori  
2 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the  
3 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away  
4 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for  
5 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,  
6 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration  
7 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,  
8 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill  
9 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill  
10 would have sought to combine Mori 2000 with the Lovaza PDR.

11 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it  
12 was known that DHA alone was responsible for the increase in LDL-C levels. Further,  
13 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or  
14 has little effect on LDL-C levels.<sup>4182</sup> Defendants identify no other basis upon which a person of  
15 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,  
16 Leigh-Firbank and/or Mori 2000.

17 (ii) The ‘560 patent Is Not Obvious Over the  
18 Omacor PDR/Lovaza PDR, in combination  
19 with Katayama and/or Matsuzawa, and/or  
20 Takaku, further in view of Nozaki and/or  
21

22 \_\_\_\_\_  
23 <sup>4181</sup> Mori 2000 at 1092.

24 <sup>4182</sup> See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

Hayashi, and further in view of Grimsgaard,  
Mori 2000 and/or Maki

With respect to the '560 patent, Defendants present a combination of nine references:

“the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki.”<sup>4183</sup>

Defendants also present charts purporting to assert that an additional 58 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 58 separate references, they additionally do not identify any motivation for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an “apparent reason” to combine must find a basis in the factual record.<sup>4184</sup> Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.<sup>4185</sup> Defendants’ contentions are no more than an assertion that certain

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<sup>4183</sup> Defendants’ Joint Invalidity Contentions at 574.

<sup>4184</sup> See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

<sup>4185</sup> See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 claim elements were known in the prior art. Throughout their contentions, Defendants’  
2 selectively cite to data points in a reference without considering other disclosures or even the  
3 reference as a whole. Each reference, however, must be evaluated for all that it teaches.<sup>4186</sup>  
4 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method  
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the  
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR  
8 further do not disclose a method to effect the claimed TG reduction without substantially  
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA  
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the  
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose  
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375  
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500  
14 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’560  
15 patent obvious and Defendants’ burden to prove otherwise is especially difficult because the  
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both  
17 generally and the Lovaza package insert specifically) during prosecution.<sup>4187</sup>

18 The analysis of the independent claims of the ’560 patent is incorporated into all asserted  
19 claims that depend from those Claims.

20 (a) A Person of Ordinary Skill Would  
21 Not Have Been Motivated to

22 <sup>4186</sup> *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 <sup>4187</sup> *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the  
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.  
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear  
and convincing standard came into play”).



3 For an invention to be obvious, there must have been an “apparent reason” to make it.  
4 The subject matter of the ‘560 patent claims would not have been obvious in light of these  
5 references because a person of ordinary skill would not have been motivated to purify EPA or  
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG  
7 levels without an increase in LDL-C levels.

8 (i) Grimsgaard, Katayama,  
9 Matsuzawa and/or Takaku  
10 Do Not Disclose Purported  
Known Clinical Benefits of  
Administering Pure EPA

11 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the  
12 “known clinical benefits of administering pure EPA - lowering triglycerides without raising  
13 LDL-C.” As discussed in Section V.I.3.c.1.a.i.a.i, incorporated herein by reference, Katayama  
14 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to  
15 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported  
16 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that  
17 the LDL-C results obtained were a clinical benefit.

18 Defendants also rely on Grimsgaard to support their assertion that “administration of  
19 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”<sup>4188</sup> However,  
20 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on  
21 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

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23 \_\_\_\_\_  
<sup>4188</sup> Defendants’ Joint Invalidity Contentions at 577.

1 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA  
2 administered to people with normal triglyceride levels for 7 weeks.<sup>4189</sup> The results from the  
3 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the  
4 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that  
5 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid  
6 supplements, which is consistent with previous studies which “suggested that serum HDL-C is  
7 better maintained with oil rich in DHA than oil rich in EPA.”<sup>4190</sup> Although Grimsgaard states  
8 that EPA may produce a small decrease in serum total cholesterol, it does not specifically  
9 comment on EPA’s effect on LDL-C.

10 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to  
11 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in  
12 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-  
13 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”<sup>4191</sup> The  
14 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the  
15 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s  
16 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to  
17 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s  
18 disclosure highlights the importance of a placebo-controlled study and why results compared  
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22 <sup>4189</sup> Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG  
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG  
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

<sup>4190</sup> Grimsgaard at 654.

<sup>4191</sup> Defendants’ Joint Invalidation Contentions at 577 n.103.

only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

TABLE 4  
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P <sup>1</sup>	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 <sup>2</sup>	-0.22 ± 0.31 <sup>2</sup>	1.23 ± 0.57	-0.15 ± 0.40 <sup>4</sup>	1.22 ± 0.55	0.11 ± 0.34 <sup>4</sup>	0.0001	0.14	0.0001	0.0001
Total cholesterol (mmol/L)	6.00 ± 0.95	0.03 ± 0.49	5.98 ± 0.94	-0.15 ± 0.55 <sup>5</sup>	6.02 ± 1.08	0.10 ± 0.55	0.01	0.04	0.4	0.004
LDL cholesterol (mmol/L)	4.06 ± 0.86	0.07 ± 0.46	4.06 ± 0.83	-0.08 ± 0.48	4.04 ± 0.98	0.06 ± 0.48	0.10	—	—	—
HDL cholesterol (mmol/L)	1.36 ± 0.30	0.06 ± 0.13 <sup>2</sup>	1.33 ± 0.31	0.01 ± 0.12	1.41 ± 0.28	-0.01 ± 0.11	0.001	0.009	0.0005	0.4
Apolipoprotein A-I (g/L)	1.38 ± 0.21	0.02 ± 0.13	1.38 ± 0.20	-0.04 ± 0.10 <sup>2</sup>	1.46 ± 0.23	0.00 ± 0.12	0.003	0.0008	0.3	0.02
Apolipoprotein B (g/L)	1.00 ± 0.21	-0.01 ± 0.11	1.01 ± 0.23	-0.03 ± 0.11 <sup>2</sup>	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 <sup>2</sup>	0.96 ± 0.13	0.04 ± 0.08 <sup>2</sup>	0.97 ± 0.12	-0.01 ± 0.06	0.0001	0.8	0.0003	0.0001
Total:HDL cholesterol	4.62 ± 1.19	-0.19 ± 0.52 <sup>2</sup>	4.70 ± 1.24	-0.13 ± 0.47 <sup>2</sup>	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

<sup>1</sup> ANOVA for between-group comparisons of change.

<sup>2</sup>  $\bar{x} \pm$  SD.

<sup>2-5</sup> One-sample t test of difference between baseline and 7 wk: <sup>3</sup> P < 0.001, <sup>4</sup> P < 0.01, <sup>5</sup> P < 0.05.

Grimsgaard concludes that both DHA and EPA lower TG levels but have “differential effects on lipoprotein and fatty acid metabolism.”<sup>4192</sup> However, Grimsgaard does not conclude that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements.”<sup>4193</sup> Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that

<sup>4192</sup> Grimsgaard at 657.

<sup>4193</sup> Grimsgaard at 654.

1 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did  
2 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and  
3 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and  
4 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified  
5 DHA results in increased LDL-C levels while administration of purified EPA resulted in a  
6 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did  
7 not have statistically significantly effects on LDL-C compared to placebo.<sup>4194</sup> A person of  
8 ordinary skill would not draw conclusions regarding differences between EPA and DHA based  
9 on statistically insignificant results.

10 Defendants also rely on Takaku to support their assertion that “clinical benefits of  
11 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the  
12 art.<sup>4195</sup> Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and  
13 safety of Epadel (of undisclosed purity)<sup>4196</sup> based on long-term administration.<sup>4197</sup>

14 A person of ordinary skill would not have concluded based on Takaku that EPA lowers  
15 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly  
16 acknowledges that “only a few subjects were examined” and cautions against drawing a  
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18 <sup>4194</sup>In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a  
19 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to  
20 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have  
21 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make  
22 such arguments for the obvious reason that it does not support their argument that EPA was known to have little or  
23 no impact on LDL-C levels.

21 <sup>4195</sup> Defendants’ Joint Invalidity Contentions at 577.

22 <sup>4196</sup> It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by  
23 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),  
24 Nakamura at 23 (Epadel with purity > 90%).

<sup>4197</sup> Takaku at ICOSAPENT\_DFNDT00006834.

1 conclusion “only from the results of the present study.”<sup>4198</sup> Because the study did not include  
2 any placebo control, a person of ordinary skill in the art would understand these reports do not  
3 provide the ability to conclude that the observed lipid effects would have occurred independent  
4 of the drug that is administered. In addition, the study was conducted exclusively in Japanese  
5 patients, and a person of ordinary skill would not have expected the results to be applicable to the  
6 general population.<sup>4199</sup>

7 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a  
8 person of ordinary skill would not have expected the results to be applicable to patients with  
9 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because  
10 measurement was not feasible due to “insufficient sample.”<sup>4200</sup> It is possible that patients with  
11 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in  
12 calculating LDL-C levels when triglyceride level is above 400 mg/dL.<sup>4201</sup> Moreover, the study  
13 does not provide different LDL-C graphs based on the baseline triglyceride levels.<sup>4202</sup> Therefore,  
14 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had  
15 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C  
16 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile  
17 throughout the study period, decreasing slightly at times but increasing by more than 8% at other  
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<sup>4198</sup> Takaku at ICOSAPENT\_DFNDT00006897.

21 <sup>4199</sup> Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results  
to other populations.”)

22 <sup>4200</sup> Takaku at ICOSAPENT\_DFNDT00006884.

23 <sup>4201</sup> See Matsuzawa at ICOSPENT\_DFNDTS00006450.

24 <sup>4202</sup> Takaku at Fig. 13, ICOSAPENT\_DFNDT00006882.

1 times.<sup>4203</sup> Because of this volatility, a person of ordinary skill would not be able to conclude  
2 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in  
3 LDL-C, stating only that the fluctuation in LDL-C was not significant.<sup>4204</sup>

4 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA  
5 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has  
6 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the  
7 administration of *fish oil* to hypercholesterolemia patients.”<sup>4205</sup> In contrast, Takaku states merely  
8 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary  
9 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study  
10 was attributable to fish oil in general, not EPA specifically.

11 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate  
12 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other  
13 studies cited by Defendants suggest that EPA increases LDL-C.<sup>4206</sup> Defendants identify no other  
14 basis upon which a person of ordinary skill would have sought to combine the Omacor  
15 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

16 (ii) Nozaki and/or Hayashi  
17 Would Not Have Rendered  
18 the Asserted Claims Obvious

18 Defendants contend that the asserted claims of the ’560 patent would have been obvious  
19 in view Nozaki and/or Hayashi in combination with other references, but they do not explain  
20 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

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22 <sup>4203</sup> Takaku at Fig. 14, ICOSAPENT\_DFNDT00006883.

23 <sup>4204</sup> Takaku at ICOSAPENT\_DFNDT00006897.

24 <sup>4205</sup> Takaku at ICOSAPENT\_DFNDT00006897.

<sup>4206</sup> See, e.g., Rambjor.

1 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a  
2 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the  
3 very high TG patient population.

4 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary  
5 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of  
6 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of  
7 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline  
8 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person  
9 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165  
10 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.  
11 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small  
12 patient population were abnormally high and would not have relied upon these results. Further,  
13 the person of skill in the art would not have looked to this patient population to predict the Apo-  
14 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of  
15 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol  
16 levels.<sup>4207</sup> Nozaki does not provide a motivation or reasonable expectation of success for  
17 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and  
18 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to  
19 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered  
20 to the very high TG patient population.

21 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of  
22 the EPA and the DHA content in the composition that was administered is unknown. A person  
23

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24 <sup>4207</sup> Nozaki at 256.