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

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

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

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

[2053] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2054] Defendants' Joint Invalidity Contentions at 532.

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

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[2055] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[2056] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with below-average levels of HDL-C levels.[2057] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,

[2055] Defendants' Joint Invalidity Contentions at 529.

[2056] Defendants' Joint Invalidity Contentions at 532.

[2057] Maki at 190.

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

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

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[2058] Maki at 191.

[2059] Maki at 195.

[2060] 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).

[2061] Maki at 197.

[2062] Maki at 197.

triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[2063]

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

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

With respect to the '399 Patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[2065] Defendants also present charts purporting to assert that an additional 60 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 60 separate references, they additionally do not suggest any identify 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

[2063] Maki at 197.

[2064] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2065] Defendants' Joint Invalidity Contentions at 529.

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

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference would cause a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a

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[2066] *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).

[2067] *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").

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

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

Defendants formulate an obviousness argument that relies on Contacos.[2069] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[2070] or "a reasonable expectation of success"[2071] of achieving the claimed invention.

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

The proposed combinations do not render the independent claim of the '399 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO

[2069] *Id.*

[2070] *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).

[2071] *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).

considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2072]

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

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

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

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

Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.D.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely confirms the safety of long term treatment of Epadel and its ability to lower both serum total 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

[2072] *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").

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

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when compared to baseline, there was no significant effect when compared to placebo.[2073] Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2074] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C.

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

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[2073] Satoh at 145.

[2074] Defendants' Joint Invalidity Contentions at 528-29.

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

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2076] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[2077] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2078] Defendants identify no other basis upon

[2075] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2076] Defendants' Joint Invalidity Contentions at 529-29.

[2077] Shinozaki at 107-109.

[2078] *See, e.g.*, Rambjor.

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

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

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

[2079] Defendants' Joint Invalidity Contentions at 532.

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

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

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

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA was the only component of fish oil to increase LDL-C. For example, there is no data comparing

[2080] Defendants' Joint Invalidity Contentions at 530.

[2081] *See* Mori 2006 at 96.

[2082] Maki at 197.

[2083] Geppert at 784.

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

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

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

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

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[2084] *Id.*

[2085] Defendants' Joint Invalidity Contentions at 530.

[2086] Kelley at 329.

[2087] Kelley at 329

cardioprotective lipoproteins" and that "DHA supplementation may improve cardiovascular health."[2088] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with 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 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy, including administration of DHA. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

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

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2089] As is the case with Kelley, Defendants use hindsight to characterize a reference based on LDL-C levels alone without considering the other lipid effects studied, considered and reported.[2090] The isolated manner in which Defendants

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[2088] Kelley at 324, 332.

[2089] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2090] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation 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.").

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

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

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

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

[2091] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

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

In any event, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would

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[2092] *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).

[2093] 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");

[2094] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[2095] *See Id.*, ¶ 17

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

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[2096]	-20%	+45%
Lovaza/Omacor[2097]	-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 the lack of motivation.

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

[2096] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2097] Chan 2002 I at 2381 (Table 3).

[2098] Defendants' Joint Invalidity Contentions at 531.

mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG reduction and the increased conversion of VLDL to LDL particles.[2099]

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

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

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[2099] *See* Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that "[t]hese 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

[2100] 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")

[2101] 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)

[2102] *See* Bays 2008 Rx Omega-3 p. 402.

C was often offset by concurrent treatment with statins.[2103] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[2104]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[2105] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[2106]

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

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[2103] *See* Harris 2008 at 14, McKenney at 722.

[2104] McKenney at 722-23.

[2105] *See* Westphal at 918, Harris 1997 at 389.

[2106] *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 chancing 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 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)").

[2107] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

[2108] McKenney 2007 at 722 (*see* Fig. 1).

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

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

[2109] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[2110] Stalenhoef at 134.

[2111] Harris 1997 at 389.

[2112] Defendants' Joint Invalidity Contentions at 531.

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

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

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[2113] *see* Section V.O.

[2114] *see* Section III.

[2115] *See, e.g.*, Defendants' Joint Invalidity Contentions at 526, 540, 556.

[2116] Defendants' Joint Invalidity Contentions at 533-34.

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

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

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

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

[2117] As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to have the same TG lowering mechanism and would have further understood that the increase in LDL-C 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[2118]	-20%	+45%
Lovaza/Omacor[2119]	-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.[2120]

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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.[2121] Epadel was available for many years prior to the invention of the '399 patent, to patients with very-high TGs as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,

[2118] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2119] Chan 2002 I at 2381 (Table 3).

[2120] 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.

[2121] 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.

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. 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.

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

[2122] Defendants' Joint Invalidity Contentions at 534.

[2123] *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.").

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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P^1	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[3]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

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 Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[2124] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[2125] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

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

[2124] *See Sanofi*, 748 F.3d at 1360–61.

[2125] *See supra* Section III.

[2126] Defendants' Joint Invalidity Contentions at 533-34.

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

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

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

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

With respect to the '399 Patent, Defendants present a combination of five references: "WO '118 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."[2128] Defendants also present charts arguing 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

[2127] Defendants' Joint Invalidity Contentions at 534.

[2128] Defendants' Joint Invalidity Contentions at 536.

combining these references.[2129, 2130] 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.[2131] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2132] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

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[2129] Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in Sections III and V.A. and B., including, the '954 publication, WO ;900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, 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 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.

[2130] 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 Invalidity Contentions at 526.

[2131] *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) (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 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).

[2132] *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").

that it teaches.[2133] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

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

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[2133] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2134] WO '118 at 9.

[2135] Defendants' Joint Invalidity Contentions at 536.

[2136] WO '118 at 22-23.

[2137] WO '118 at 8.

patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[2138]

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

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

[2138] *See* Section III.

[2139] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

[2140] WO '118 at 22-23.

[2141] WO '118 at 23.

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

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

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

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge

[2142] *See, e.g.*, '900 Pub. at 16-17.

[2143] '900 Pub. at 5.

[2144] '900 Pub. at 39.

[2145] *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").

that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[2146]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. 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.[2147] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2148] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

[2146] Defendants' Joint Invalidity Contentions at 536.

[2147] *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).

[2148] *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").

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

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

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

[2149] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

View of Katayama, Matsuzawa and/or Takaku.

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."[2150] 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.[2151] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2152] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

[2150] Defendants' Joint Invalidity Contentions at 536.

[2151] *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).

[2152] *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").

Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2153] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[2154] 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

[2153] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2154] Defendants' Joint Invalidity Contentions at 537.

record.[2155] Defendants' assertions related to motivation are insufficient,[2156] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[2157] or "a reasonable expectation of success"[2158] of achieving the claimed invention. Therefore, Defendants should be precluded from relying on this these references.

As discussed above in Section V.D.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only designed to confirm the safety of long term treatment of Epadel and its ability to lower both

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[2155] *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).

[2156] 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.

[2157] *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).

[2158] *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).

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

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

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

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

[2159] Takaku at ICOSAPENT_DFNDT00006897.

[2160] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[2161] *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").

Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[2162]

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

[2162] Defendants' Joint Invalidity Contentions at 537.

[2163] 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.

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

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

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

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

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[2164] Maki at 195.

[2165] 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.").

[2166] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2167] Defendants' Joint Invalidity Contentions at 537.

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

Indeed, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[2168]	-20%	+45%
Lovaza/Omacor[2169]	-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

[2168] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2169] Chan 2002 I at 2381 (Table 3).

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."[2170] 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.[2171] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not."[2172] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[2173] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with other saturated and polyunsaturated fatty acids.[2174] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[2175] Kelley does not show that

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[2170] Defendants' Joint Invalidity Contentions at 538.

[2171] 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.

[2172] Defendants' Joint Invalidity Contentions at 542.

[2173] The discussion related to Leigh-Firbank in Section V.D.3.c.1.a.i.a.iii is incorporated herein by reference.

[2174] The discussion related to Kelley in Section V.D.3.c.1.a.iii.a.ii is incorporated herein by reference.

[2175] *See* Mori 2006 at 96.

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

[2176] Kelley at 329.

[2177] 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.")

[2178] *See* Mori 2006 at 96.

[2179] Defendants' Joint Invalidity Contentions at 538.

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

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

[2180] Mori 2000 at 1092.

[2181] 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.

[2182] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[2183] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[2184] Harris 2008 at 13.

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

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that DHA is *more* cardioprotective than EPA.[2187] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[2188] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[2189] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[2190] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA

[2185] Defendants' Joint Invalidity Contentions at 538-39.

[2186] 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").

[2187] Harris 2007 at 8.

[2188] *Id.*

[2189] 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.").

[2190] *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 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.").

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

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

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[2193] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[2194] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG

[2191] Defendants' Joint Invalidity Contentions at 546.

[2192] Defendants' Joint Invalidity Contentions at 540.

[2193] *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.").

[2194] Nakamura, Matsuzawa, and Takaku.

levels > 500 mg/dL."[2195,2196] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one patient had a baseline TG level > 500 mg/dL.[2197] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[2198] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[2199] Based on this disclosure, only one patient definitively had a baseline TG level ≥ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[2200] In Takaku, three patients had baseline TG levels above 500 mg/dL.[2201] However, the mean baseline TG level for all patients was 245 mg/dL.[2202] Indeed, the mean baseline TG level of the patients in all three studies was well below

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[2195] Defendants' Joint Invalidity Contentions at 539.

[2196] 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.

[2197] Nakamura at 23, Table 1.

[2198] Nakamura at 23, Tables 1 and 2.

[2199] *Id.* at 23.

[2200] *Id.* at 10.

[2201] Takaku at ICOSAPENT_DFNDTS00006895.

[2202] Takaku at ICOSAPENT_DFNDTS00006875.

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

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

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

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[2203] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

[2204] Defendants' Joint Invalidity Contentions at 540.

[2205] Mori 2006 at 98.

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

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[2208] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

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

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[2206] Defendants' Joint Invalidity Contentions at 544.

[2207] 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 grater with DHA supplementation than EPA supplementation).

[2208] Defendants' Joint Invalidity Contentions at 540.

[2209] Defendants' Joint Invalidity Contentions at 540-41.

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

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

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

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

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[2210] *See* Section III.

[2211] Defendants' Joint Invalidity Contentions at 541.

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

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

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[2215] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that

[2212] Defendants' Joint Invalidity Contentions at 542.

[2213] Defendants' Joint Invalidity Contentions at 542.

[2214] *See* Section IV.

[2215] Defendants' Joint Invalidity Contentions at 544.

the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[2216]

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

[2216] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese 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.

[2217] Defendants' Joint Invalidity Contentions at 544.

[2218] 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").

[2219] Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

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

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

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

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[2222] Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo."[2223] However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of

[2220] *see* Section V.O.

[2221] *see* Section III.

[2222] Defendants' Joint Invalidity Contentions at 537.

[2223] Defendants' Joint Invalidity Contentions at 541 .

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

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

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering agents, specifically fibrates and

[2224] Defendants' Joint Invalidity Contentions at 545.

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[2225]	-20%	+45%
Lovaza/Omacor[2226]	-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 using EPA.

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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 '399 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.

[2225] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2226] Chan 2002 I at 2381 (Table 3).

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.

(2) Dependent Claims

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

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 combined to teach the administration of the claimed EPA to very high TG patients.[2227] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2228] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2229]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not

[2227] *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").

[2228] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2229] *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").

show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[2230]

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

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

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 3.

Defendants contend, without providing meaningful support, that the claim element was well known in the art. 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

[2230] *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)).

[2231] *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.")

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. Defendants make a conclusory statement that the claimed method of treatment was well known in the art, but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[2232] Further Defendants cite to the "Lovaza product" without identifying the prior art reference to which they refer. Such a reference is inadequate.

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[2233] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

[2232] *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)).

[2233] *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.")

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

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 4.

Defendants contend that it would be obvious that a person receiving the claimed EPA compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) 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 2) 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. Defendants merely demonstrate that the element was purported known in the prior art without explaining how it can be combined with other elements.[2234] As such,

[2234] *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").

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

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

[2235] *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").

[2236] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2237] *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").

[2238] *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)).

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

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

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 5.

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

[2239] *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.")

[2240] *Id.*

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. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be combined.[2241] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[2242] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each prior art reference as a whole.[2243] Each reference must be evaluated for all that it teaches.

[2241] *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").

[2242] *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").

[2243] *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).

Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2244]

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

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for

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[2244] *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").

[2245] *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)

[2246] *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)).

treating the recited patient population.[2247] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

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

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 Claims 6 and 7.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[2248] 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

[2247] *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.")

[2248] 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.

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 further contend, without support, that a person of ordinary skill would "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude, without support, that it would have been obvious to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing triglycerides while avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) 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 3) 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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[2249] As such, Defendants discuss the claim elements in isolation, and fail to address

[2249] *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").

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

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

[2250] *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").

[2251] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2252] *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").

[2253] *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)).

attached to the recited TG reduction amount.[2254] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

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

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

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 8.

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

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[2254] 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).

[2255] *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).

[2256] *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.").

the art to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. 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 combined to teach the administration of the claimed EPA to very high TG patients.[2257] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2258] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2259]

[2257] *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").

[2258] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2259] *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").

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

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[2261] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

Defendants cite only one reference in their invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that "it was known that Apo-B is a component of LDL-C." Defendants cite to no passage or page of Theobald in connection with that argument and no support for their argument that Theobald makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all atherogenic lipoproteins.[2262]

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

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[2260] *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)).

[2261] *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.")

[2262] June 26, 2012 Bays Declaration; *see also* Section III.

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

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Crypthecodinium 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:[2263]

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

	DHA		Placebo		
	Before treatment	After treatment	Before treatment	After treatment	Treatment effect[1]
Total cholesterol (mmol/L)	5.15 ± 0.145[2]	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42)[3]
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)[4]
HDL cholesterol (mmol/L)[5]	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)[6]	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	−0.18 (−0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)[7]
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)[3]
Weight (kg)[8]	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (−0.85, 0.24)

[1] Mean difference between active treatment and placebo; 95% CI in parentheses.
[2] $\bar{x}$ ± SEM (all such values); $n = 38$.
[3,4,7] Paired t test: [3] $P = 0.04$, [4] $P = 0.004$, [7] $P = 0.03$.
[5] HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.
[6] $n = 37$; data were log transformed before analysis by paired t test.
[8] Weight increased over the entire study period. Significant order × time effect, $P = 0.001$.

[2263] Theobald at 561, table 3.

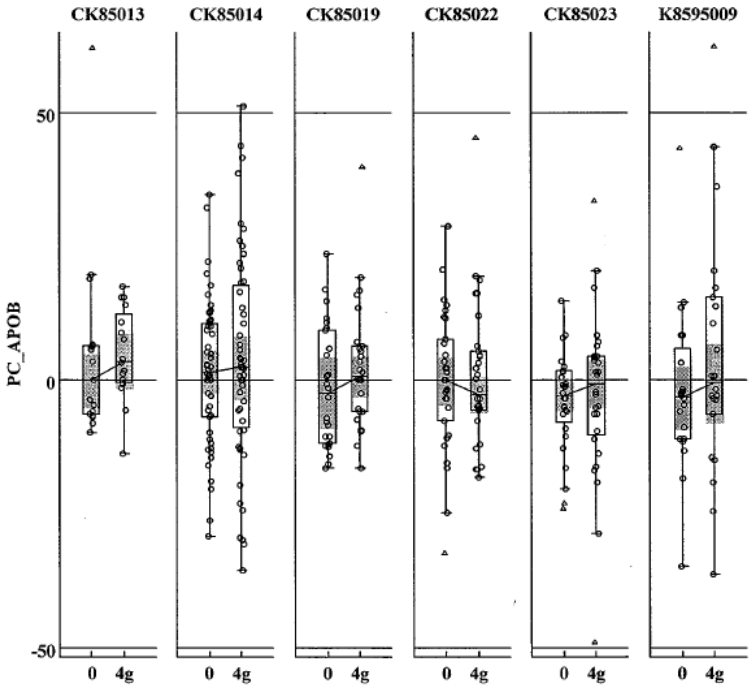
As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases 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 Apo-B levels in patients with very high TG levels.[2264] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[2265]

[2264] May 8, 2012 Bays Declaration.

[2265] Lovaza Approval Package at Table 14.

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

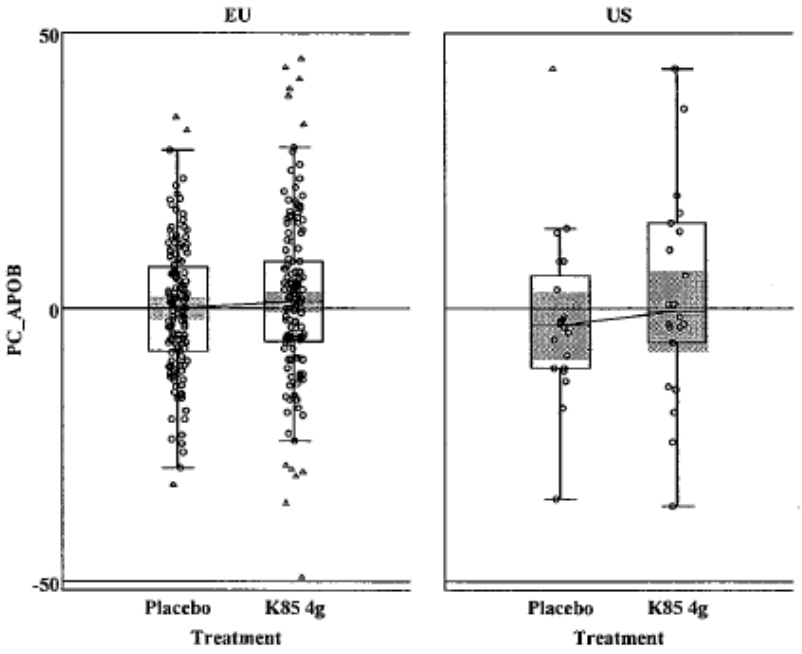


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[2266] there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza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

[2266] The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

[2267] 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.[2268] 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

[2268] *See* Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

those references, also reflecting a lack of motivation and no reasonable expectation of success.[2269]

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

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

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

[2269] Defendants' Contentions at 236.

[2270] ATP-III at 3170; Bays 2008 I at 395.

[2271] Kwiterovich in Kwiterovich at 4.

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.D.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 9.

Defendants contend that it would have been obvious to use the claimed composition to reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy. 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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[2272] As such, Defendants fail

[2272] *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)).

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

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

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

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

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

[2273] 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 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.

[2274] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

[2275] *Id.* at 2129.

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[2276] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[2277] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[2278] Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

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

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

[2277] *See, e.g.*, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim 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).

[2278] *See generally* the '399 patent and its prosecution history.

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

Defendants further allege that the term "who have not received . . . a concurrent lipid altering therapy" is indefinite. Defendants provide no basis for this allegation. In light of the specification and the prosecution history, however, a person of ordinary skill in the art would understand with reasonable certainty the scope of a "concurrent lipid altering therapy."[2281] For example, it was known that Lovaza was prescribed along with statin. Therefore, the phrase "concurrent lipid altering therapy" does not render the claim indefinite.

Defendants further contend that the metes and bounds of the phrase "without substantially increasing LDL-C" are unclear. Defendants do not provide the basis for the assertion other than stating that it is unclear and the specification does not clarify its meaning. As discussed above, use of the phrase "substantially" does not render a claim *per se* indefinite. In light of the specification and the prosecution history, a person of ordinary skill in the art

[2279] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. 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, 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").

[2280] *See generally* the '399 patent and its prosecution history.

[2281] *See generally* the '399 patent and its prosecution history.

would know with reasonable certainty the scope of the term "without substantially increasing LDL-C" and therefore does not render the claims indefinite.[2282]

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

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

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[2282] *See generally* the '399 patent and its prosecution history.

[2283] *Novo Indus., L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354, 1357 (Fed. Cir. 2003). These "determinations 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).

[2284] *See generally* the '399 patent and its prosecution history.

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

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

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

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

[2285] 35 U.S.C. § 271(c) (emphasis added).

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

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

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[2286] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[2287] *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).

[2288] *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.

[2289] *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

[2290] *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.

[2291] *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."); *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.").

[2292] *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").

[2293] *See* U.S. Provisional Application No. 61/151,291.

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

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the dosages and quantities of the claimed methods.[2294] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[2295] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[2296] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such

[2294] *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."); *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.").

[2295] *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").

[2296] *See* U.S. Provisional Application No. 61/151,291.

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

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

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[2297] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[2298]

[2297] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

[2298] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is 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

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

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

The first paragraph of 35 U.S.C. § 112 requires that the specification "enable any person skilled in the art . . . to make and use [the claimed invention]." A claim is not enabled if it would require undue experimentation for a person of ordinary skill to make or use the invention. Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[2299] The enablement requirement is separate and distinct from the written description requirement,[2300] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[2301]

Defendants make two specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary

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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.").

[2299] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[2300] *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[2301] MPEP § 2164.

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

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

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

[2302] *See* VASCEPA Prescribing Information at Table 2.

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

E. **The '677 Patent**

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

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

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

[2303] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical 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.").

[2304] *See* May 16, 2011 Bays Declaration at Appendix B.

[2305] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[2306] 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).

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

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

[2307] *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) ("First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts.").

[2308] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

[2309] *Mayo*, 132 S. Ct. at 1294.

[2310] *Id.* at 1301.

[2311] *Id.*

[2312] *Id.* at 1302 (contrasting the patent-ineligible claims of that case to "a typical patent on a new drug or a new way 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).

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

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[2316] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[2317] To say that the claims of the '677 patent claim a law of

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[2313] *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).

[2314] *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).

[2315] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

[2316] *See* Defendants' Joint Invalidity Contentions at 299.

[2317] See *CellzDirect*, 827 F.3d at 1048-49 ("The [asserted] claims are like thousands of others that recite processes 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).").

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

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

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In

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[2318] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

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

[2320] *See Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

[2321] *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 "just one step in the whole process" claimed by the invention).

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

2. The Asserted Claims of the '677 Patent Are Not Anticipated by WO '118

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

[2322] *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

[2323] *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).

[2324] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[2325] *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).

[2326] *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).

and the breadth of the claims.[2327] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[2328]

Defendants assert that Claims 1-9 of the '677 Patent are anticipated by the WO '118 reference.[2329]

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

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

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

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

[2327] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[2328] *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).

[2329] 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.

[2330] *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).

[2331] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[2332] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

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

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[2333] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated

[2332] Defendants' Invalidity Contentions at 202-204.

[2333] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

limitation."[2334] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[2335] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claim every time it is administered.

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

Therefore, WO '118 cannot anticipate the independent claim of the '677 patent. Because the dependent claims include all of the claim elements of the independent claim, WO' 118 cannot anticipate any of the dependent claims as well.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

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

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

[2335] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[2336] *See, e.g.*, Rambjor.

until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[2337] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[2338]

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

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[2339] The recitation of a "method of reducing triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

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

[2338] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

[2339] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer 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").

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[2340] Thus, the entire preamble in the independent claim of the '677 must contain patentable weight.

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

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina."[2341] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[2342] WO '118 does not expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claim.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of

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[2340] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

[2341] WO '118 at 12.

[2342] *Id.*

the reference.[2343] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

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

[2343] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

[2344] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

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

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

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as compared to the patent's claimed range of 0.1 to 5.0 percent.[2347] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap

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[2345] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[2346] *Atofina*, 441 F.3d at 1000.

[2347] *Id.*

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

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

[2348] *Id.*

[2349] *See* Section III.

[2350] *Id.*

[2351] ATP III at 3335; *See also* Section III.

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

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

[2352] *Id.*

[2353] *Id.*

[2354] *Id.*

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

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

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

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic

range of 330 to 450 °C,"[2355] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[2356] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[2357] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '677 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '677 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '677 patent and cannot anticipate the independent claim of the '677 Patent.

WO '118 further does not anticipate the claims of the '677 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[2358] Therefore, WO '118 discloses

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[2355] *Atofina*, 441 F.3d at 1000.

[2356] *Id.*

[2357] *Id.*

[2358] WO '118 at 22.

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

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[2359] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[2360] and therefore failed to anticipate the claimed range.[2361] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[2362] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[2363]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '677 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '677 patent. Therefore, WO '118's broad

[2359] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[2360] *Atofina*, 441 F.3d at 1000.

[2361] *Atofina*, 441 F.3d at 1000.

[2362] *Id.*

[2363] *Id.*

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

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

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

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

[2364] WO '118 at 22.

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

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

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

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

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

3. The Claims of the '677 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '677 Patent obvious.[2368] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '677 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of

[2365] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[2366] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[2367] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[2368] Defendants' Joint Invalidity Contentions at 13-25.

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

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

- 1) ". . .the asserted claims of the '677 patent would have been obvious over 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."

- 2) ". . .the asserted claims of the '677 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified 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."

- 3) ". . .the asserted claims of the '677 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '677 patent would have been obvious over WO '118 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."

[2369] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention 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))).

[2370] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, 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 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.

- 5) ". . . the asserted claims of the '677 patent would have been obvious over 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."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[2371] 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.[2372]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[2373] Indeed, any teaching in the art that points away from the claimed invention must be considered.[2374] A reference teaches away if a person of ordinary skill, upon reading 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.[2375] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[2376]

[2371] 35 U.S.C. § 103(a).

[2372] *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).

[2373] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2374] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

[2375] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[2376] *Id*.

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

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[2380] "[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."[2381] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[2382]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[2383] or to modify a prior art reference in a way that

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[2377] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[2378] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[2379] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

[2380] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[2381] *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))

[2382] *KSR*, 550 U.S. at 418-419.

[2383] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

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

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[2388] and "a reasonable expectation of success."[2389]

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[2390] This protects against the use of hindsight to pick through the prior art

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[2384] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[2385] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[2386] *Id*. at 88.

[2387] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

[2388] *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).

[2389] *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).

[2390] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; 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).

based solely on structural similarity to the claimed compound.[2391] Any assertion of an "apparent reason" must find a basis in the factual record.[2392]

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[2393] including those discovered after the patent was filed or even issued.[2394] "The basic principle behind this rule is straight-forward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[2395] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[2396]

[2391] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (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).

[2392] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[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*, 619 F.3d at 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 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").

[2393] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [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.").

[2394] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

[2395] *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.").

[2396] *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

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

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[2402]

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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.'").

[2397] *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).

[2398] *Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1569 (Fed. Cir. 1987).

[2399] *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.

[2400] *Graham*, 383 U.S. at 36.

[2401] *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)).

[2402] *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.").

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

a) General Overview

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

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[2404] Defendants

[2403] Mori 2006 at 96.

[2404] Defendants' Joint Invalidity Contentions at 310 (*see* FN 46).

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

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

[2405] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 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).

[2406] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

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

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

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

[2407] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

[2408] *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).

[2409] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

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

Fibrate	**Mean Baseline TG Value**	**TG**	**LDL-C**	**HDL-C**	**Total-C**
Tricor (fenofibrate)[2414]	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*

[2410] *Id.*

[2411] *Id. See also*, Trilipix Label at 27.

[2412] *Id. See also*, Trilipix Label at 27.

[2413] *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).

[2414] 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.[2415] It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.[2416] 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%.[2417] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[2418]

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

[2415] Chan 2002 I at 2379-81.

[2416] *Id.; See also*, Westphal at 918.

[2417] *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

[2418] *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 [cholesteryl 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.)"

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

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the pharmacologic properties of the ethyl EPA compound identified in the claims of the '677 patent are inherent to the compound when administered to a human subject."[2421] Inherency may not

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[2419] Bays May 16, 2011 Decl., ¶ 11 (noting the "general knowledge in the art that omega-3 fatty acids as a class increase LDL-C" in very-high TG patients); McKenney 2007, at 724 ("Because of the increase in LDL levels 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.").

[2420] Bays 2008 I at 400-402.

[2421] Defendants' Joint Invalidity Contentions at 311.

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

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

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[2422] *See, e.g.*, *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) ("A party must . . . 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).

[2423] *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.").

[2424] *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

[2425] Defendants' Joint Invalidity Contentions at 312.

[2426] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

[2427] Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

"unexpected and improved effects of administration of the claimed compound."[2428] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

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

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

(1) WO '118

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

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

[2428] 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).

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

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

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

(2) WO '900

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

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

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

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

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

(3) Contacos

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

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

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

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

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

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

(4) Grimsgaard

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

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

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

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

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

(5) Hayashi

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

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

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

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

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

(6) Katayama

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

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

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

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

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

(7) Leigh-Firbank

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

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

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

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

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

(8) Lovaza PDR

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

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

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

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

(9) Maki

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

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

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

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

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

(10) Matsuzawa

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

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

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

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

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

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

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

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

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

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

(12) Mori 2006

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

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

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

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

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

(13) Nozaki

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

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

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

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

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

recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

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

(14) Omacor PDR

The Omacor PDR is the Physicians' Desk Reference describing Omacor.

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

With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR further does not disclose or

suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

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

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

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

With respect to Claim 1 of the '677 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG levels. Satoh further does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Satoh further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially

increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

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

(16) Shinozaki

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

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

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

does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. Shinozaki further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

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

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '677 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Takaku further do not disclose or suggest these elements because they do not disclose or suggest the claimed pharmaceutical

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

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

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

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '677 Patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims.

Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '677 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 1 (and therefore Claims 2-9): *administering the claimed pharmaceutical composition to the recited subject to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control*. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '677 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '677 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claim of the '677 Patent Would Have Been Obvious

(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 '677 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 '677 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."[2429] 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.[2430, 2431] 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.[2432] Defendants' unsupported cobbling

[2429] Defendants' Joint Invalidity Contentions at 305.

[2430] 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, Mataki, 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 Invalidity Contentions at 304-05.

[2431] 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 Invalidity Contentions at 303-04.

[2432] *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).

of selective disclosures represents hindsight reconstruction.[2433] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2434] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claim of the '677 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2435]

[2433] *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").

[2434] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2435] *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.

The analysis of the independent claim of the '677 Patent is incorporated into all asserted claims that depend from this Claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active **Ingredient in Lovaza with Pure EPA**

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '677 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.[2436] As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with

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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").

[2436] *See* Grimsgaard at 652 (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.)

lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-high or high TG patients, was expected. At the priority date of the '677 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[2437] This is an incorrect characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C

[2437] Defendants' Joint Invalidity Contentions at 305 and 306.

levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2438] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[2439] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[2440]

[2438] Defendants' Joint Invalidity Contentions at 305.

[2439] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI_2 and PGI_3 Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[2440] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2441] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[2442] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[2443] Katayama does not disclose *any* LDL-C related data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[2444] In addition to Katayama's lack of disclosure regarding LDL-C,

[2441] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2442] Defendants' Joint Invalidity Contentions at 305 and 306.

[2443] Katayama at 2.

[2444] *Id.* at 16.

Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[2445] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[2446] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[2447] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[2448] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than

[2445] Defendants' Joint Invalidity Contentions at 305 and 306.

[2446] Matsuzawa at 7 and 19.

[2447] *Id.* at 23.

[2448] *Id.* at 10.

the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[2449] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[2450] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify

[2449] *Id.* at 11.

[2450] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2451] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '677 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '677 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person

[2451] *See, e.g.*, Rambjor.

of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[2452] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[2453] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,

[2452] Nozaki at 256.

[2453] Hayashi at 26, Table I.

to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2454] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that

[2454] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2455] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either

[2455] Defendants' Joint Invalidity Contentions at 308.

EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[2456] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[2457] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[2458] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-

[2456] Mori 2006 at 96.

[2457] Leigh-Firbank at 440.

[2458] *See, e.g.* Grimsgaard at 654.

C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "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."[2459] Although teaching away is fact-dependent, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[2460]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[2461] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[2462] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[2463] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA,

[2459] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[2460] *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.").

[2461] Mori 2000 at 1092.

[2462] Mori 2000 at 1088.

[2463] Mori 2000 at 1092.

despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2464] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '677 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or Hayashi, and Further in View of Grimsgaard, Mori 2000 and/or Maki

With respect to the '677 Patent, Defendants present a combination of nine references: "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified 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."[2465] 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

[2464] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2465] Defendants' Joint Invalidity Contentions at 305-06.

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.[2466] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2467] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2468] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA

[2466] *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).

[2467] *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").

[2468] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claim of the '677 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2469]

The analysis of the independent claim of the '677 Patent is incorporated into all asserted claims that depend from this Claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '677 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported

[2469] *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").

Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.E.3.c.1.a.i.a.i, incorporated herein by reference, Katayama and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[2470] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[2471] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[2472] Although Grimsgaard states

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[2470] Defendants' Joint Invalidity Contentions at 309.

[2471] Defendants state in their Joint Invalidity Contentions at 297 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).

[2472] Grimsgaard at 654.

that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in 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."[2473] 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' 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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[5]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[2474] However, Grimsgaard does not conclude

[2473] Defendants' Joint Invalidity Contentions at 309 n.43.

[2474] Grimsgaard at 657.

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."[2475] 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 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard 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." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[2476] A person of

[2475] Grimsgaard at 654.

[2476] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to 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.

ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[2477] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[2478] based on long-term administration.[2479]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[2480] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[2481]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with

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[2477] Defendants' Joint Invalidity Contentions at 306.

[2478] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[2479] Takaku at ICOSAPENT_DFNDT00006834.

[2480] Takaku at ICOSAPENT_DFNDT00006897.

[2481] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[2482] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[2483] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[2484] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other times.[2485] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[2486]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[2487] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary

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[2482] Takaku at ICOSAPENT_DFNDT00006884.

[2483] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[2484] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

[2485] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[2486] Takaku at ICOSAPENT_DFNDT00006897.

[2487] Takaku at ICOSAPENT_DFNDT00006897.

skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2488] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '677 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

[2488] *See, e.g.*, Rambjor.

Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[2489] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[2490] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[2489] Nozaki at 256.

[2490] Hayashi at 26, Table I.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2491] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2492] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

[2491] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2492] Defendants' Joint Invalidity Contentions at 308.

known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or Maki —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[2493] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[2494] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with

[2493] Defendants' Joint Invalidity Contentions at 306.

[2494] Defendants' Joint Invalidity Contentions at 308-09.

below-average levels of HDL-C levels.[2495] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated, monounsaturated and polyunsaturated fatty acids.[2496] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[2497] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have also contributed to the elevation in LDL cholesterol."[2498] Further, Maki admits that the "mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[2499] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Defendants mischaracterize the rise in LDL-C associated with the administration of omega-3 fatty acids as being a "negative effect" because they incorrectly focus on only the LDL-C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in LDL-C to be troublesome; Maki states that "the lack of increase in the total/HDL cholesterol ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level

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[2495] Maki at 190.

[2496] Maki at 191.

[2497] Maki at 195.

[2498] 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).

[2499] Maki at 197.

less worrisome."[2500] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[2501]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2502] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(iii) The '677 Patent is not Prima Facie Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or in View of Satoh or Shinozaki in Further View of Contacos

With respect to the '677 Patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[2503] Defendants also present charts purporting to assert that an additional 60 references may be combined in order to render the Claims obvious. Not only do

[2500] Maki at 197.

[2501] Maki at 197.

[2502] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2503] Defendants' Joint Invalidity Contentions at 306.

Defendants ignore the improbability that a person of ordinary skill would combine 60 separate references, they additionally do not suggest any identify 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.[2504] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2505] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2506] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method

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[2504] *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).

[2505] *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").

[2506] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference would cause a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels.

Defendants formulate an obviousness argument that relies on Contacos.[2507] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[2508] or "a reasonable expectation of success"[2509] of achieving the claimed invention.

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

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[2507] *Id.*

[2508] *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).

[2509] *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).

any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C.

The proposed combinations do not render the independent claim of the '677 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2510]

The analysis of the independent claim of the '677 Patent is incorporated into all asserted claims that depend from this Claim.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '677 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

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

Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As

[2510] *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").

discussed in Section V.E.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely confirms the safety of long term treatment of Epadel and its ability to lower both serum total 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 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when compared to baseline, there was no significant effect when compared to placebo.[2511] Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2512] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C.

[2511] Satoh at 145.

[2512] Defendants' Joint Invalidity Contentions at 305.

Further, Satoh was a small study conducted in only Japanese patients. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2513] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2514] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[2515] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

[2513] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2514] Defendants' Joint Invalidity Contentions at 305.

[2515] Shinozaki at 107-109.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2516] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki and/or Contacos.

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2517] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement do not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels, respectively. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or Kelley —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a

[2516] *See, e.g.*, Rambjor.

[2517] Defendants' Joint Invalidity Contentions at 308.

person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

Defendants rely on Geppert and/or Kelley to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[2518] Both Geppert and Kelley administer DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids. Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[2519] For example, Defendants' own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.[2520]

In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[2521] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA

[2518] Defendants' Joint Invalidity Contentions at 306.

[2519] *See* Mori 2006 at 96.

[2520] Maki at 197.

[2521] Geppert at 784.

was the only component of fish oil to increase LDL-C. For example, there is no data comparing DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying explain the mechanism of LDL-C increase.[2522] A person of ordinary skill would have not expected that EPA and DHA would have different effects on LDL-C based on Geppert.

Defendants contend that Kelley shows that DHA was responsible for the increase in LDL-C.[2523] In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[2524] Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in context with the other lipid effects reported in the study. Kelley states that:

> DHA supplementation may lower the risk of CVD by reducing plasma triacylglycerols; triaclyglycerol:HDL; the number of small, dense LDL particles; and mean diameter of VLDL particles. An increase was observed in fasting LDL cholesterol, but it is unlikely this increase is detrimental because no increase was observed in the overall number of LDL particles; actually, there was an 11% reduction that was statistically not significant. The reason LDL cholesterol increased despite no change in LDL particle number was that the LDL particles were made larger and hence more cholesterol rich by DHA treatment.[2525]

Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Kelley's ultimate conclusion is that "[o]verall, DHA supplementation reduced the

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[2522] *Id.*

[2523] Defendants' Joint Invalidity Contentions at 306.

[2524] Kelley at 329.

[2525] Kelley at 329

concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins" and that "DHA supplementation may improve cardiovascular health."[2526] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with 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 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy, including administration of DHA. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

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

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2527] As is the case with Kelley, Defendants use hindsight to characterize a reference based on LDL-C levels alone without considering the other

[2526] Kelley at 324, 332.

[2527] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

lipid effects studied, considered and reported.[2528] The isolated manner in which Defendants select such data points is not the approach that a person of ordinary skill would have taken at the time of the invention. Defendants' approach represents the use of impermissible hindsight bias. A person of ordinary skill would take into consideration the entire disclosure of a reference, including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a favorable effect in hypertriglyceridemic patients.

Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2529] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert and/or Kelley.

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

Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,

[2528] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation 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.").

[2529] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[2530] Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[2531] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[2532] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[2533] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

In any event, a person of ordinary skill in the art would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high

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[2530] *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).

[2531] 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");

[2532] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[2533] *See Id.*, ¶ 17

TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[2534]	-20%	+45%
Lovaza/Omacor[2535]	-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 the lack of motivation.

Defendants offer no "apparent reason" to administer EPA as claimed to patients with fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on Lovaza/Omacor as the starting point to "find a therapy that would reduce TG levels in patients with TG levels ≥ 500 mg/dL without negatively impacting LDL-C levels."[2536] Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500 mg/dL but

[2534] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2535] Chan 2002 I at 2381 (Table 3).

[2536] Defendants' Joint Invalidity Contentions at 308.

significantly increases LDL-C--an effect understood to be a consequence of TG reduction and the increased conversion of VLDL to LDL particles.[2537]

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[2538] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[2539] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels the most in patients with the highest pretreatment TG levels.[2540] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-

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[2537] *See* Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that "[t]hese 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

[2538] 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")

[2539] 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)

[2540] *See* Bays 2008 Rx Omega-3 p. 402.

C was often offset by concurrent treatment with statins.[2541] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[2542]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[2543] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[2544]

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[2545] Correspondingly, prescription omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[2546] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net

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[2541] *See* Harris 2008 at 14, McKenney at 722.

[2542] McKenney at 722-23.

[2543] *See* Westphal at 918, Harris 1997 at 389.

[2544] *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 chancing 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 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)").

[2545] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

[2546] McKenney 2007 at 722 (*see* Fig. 1).

effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the number of small, dense LDL particles to larger LDL particles.[2547] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[2548] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[2549]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[2550] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

[2547] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[2548] Stalenhoef at 134.

[2549] Harris 1997 at 389.

[2550] Defendants' Joint Invalidity Contentions at 307-08.

reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[2551] (which is a reflection of total atherogenic lipoproteins)[2552] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention.[2553] Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population, they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

[2551] *see* Section V.O.

[2552] *see* Section III.

[2553] *See, e.g.*, Defendants' Joint Invalidity Contentions at 303, 317, and 333.

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

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

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

Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by combining the references cited by defendants. For a particular combination of references, there must be a reasonable expectation that the combination will produce the claimed invention. In this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG levels.[2554] A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG patient population. As discussed in Section III and above, it was well known that TG-lowering

[2554] As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to have the same TG lowering mechanism and would have further understood that the increase in LDL-C 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[2555]	-20%	+45%
Lovaza/Omacor[2556]	-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.[2557]

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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.[2558] 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,

[2555] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2556] Chan 2002 I at 2381 (Table 3).

[2557] 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.

[2558] 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.

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. 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.

Defendants argue that because Grimsgaard administered purified ethyl EPA to patients with borderline-high/high TG, it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of 2.7 grams of purified EPA to patients with >500 mg/dL TG by Matsuzawa.[2559] Defendants' contentions are no more than a demonstration that certain claim elements was known in the prior art and demonstrates impermissible hindsight reconstruction.[2560] As is reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA, EPA, and control in terms

[2559] Defendants' Joint Invalidity Contentions at 310.

[2560] *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.").

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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[3]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

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 Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[2561] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[2562] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

Defendants argue that a person of ordinary skill at the time of the invention, based on studies in normal, borderline-high and high TG patients, knew that administration of DHA alone resulted in undesirable increased LDL-C levels while administration of EPA alone had little to no impact on LDL-C levels.[2563] However, that statement does not conform with what was known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor

[2561] *See Sanofi*, 748 F.3d at 1360–61.

[2562] *See supra* Section III.

[2563] Defendants' Joint Invalidity Contentions at 309.

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

With the lack of any reasonable expectation of success, Defendants argue that their proposed combination amounts to a simple substitution of one known element for another, and that that these changes yield predictable results.[2564] Such an argument, however, represents pure and impermissible hindsight bias and further does not consider that reasons for which a person of ordinary skill would not be motivated to combine these references and affirmatives ways in which the art taught away from these combinations.

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

(i) The '677 Patent is not Obvious Over WO '118 or WO '900, in Combination with the Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '677 Patent, Defendants present a combination of five references: "WO '118 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."[2565] Defendants also present charts arguing 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

[2564] Defendants' Joint Invalidity Contentions at 311.

[2565] Defendants' Joint Invalidity Contentions at 312-13.

combining these references.[2566, 2567] 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.[2568] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2569] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

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[2566] Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, 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 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.

[2567] 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 Invalidity Contentions at 303.

[2568] *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) (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 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).

[2569] *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").

that it teaches.[2570] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[2571] Contrary to Defendants' assertion that WO '118 discloses "the administration of 4 g of pure EPA with no DHA,"[2572] WO '118 fails to disclose the claimed subject with the specified very high TG levels (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[2573]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[2574] WO '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

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[2570] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2571] WO '118 at 9.

[2572] Defendants' Joint Invalidity Contentions at 313.

[2573] WO '118 at 22-23.

[2574] WO '118 at 8.

patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[2575]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[2576] WO '118 states that "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[2577] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[2578] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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

[2575] *See* Section III.

[2576] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

[2577] WO '118 at 22-23.

[2578] WO '118 at 23.

WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[2579] Moreover, WO '900 does not teach the desired effect of EPA other than commenting generally that it "may promote health and ameliorate or even reverse the effects of a range of common diseases."[2580] It has no discussion, for example, on any TG-lowering effect of EPA. Although WO '900 identifies DHA as an "undesired molecule", it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than commenting generally that "the desired effects of EPA may be limited or reversed" by them.[2581] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claim of the '677 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2582]

The analysis of the independent claim of the '677 patent is incorporated into all asserted claims that depend from this Claim.

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge

[2579] *See, e.g.*, '900 Pub. at 16-17.

[2580] '900 Pub. at 5.

[2581] '900 Pub. at 39.

[2582] *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").

that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[2583]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. 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.[2584] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2585] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

[2583] Defendants' Joint Invalidity Contentions at 313.

[2584] *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).

[2585] *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").

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

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2586] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '677 Patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in

[2586] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

View of Katayama, Matsuzawa and/or Takaku.

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."[2587] 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.[2588] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2589] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

[2587] Defendants' Joint Invalidity Contentions at 313.

[2588] *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).

[2589] *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").

Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2590] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[2591] 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

[2590] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2591] Defendants' Joint Invalidity Contentions at 313.

record.[2592] Defendants' assertions related to motivation are insufficient,[2593] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[2594] or "a reasonable expectation of success"[2595] of achieving the claimed invention. Therefore, Defendants should be precluded from relying on this these references.

As discussed above in Section V.E.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only designed to confirm the safety of long term treatment of Epadel and its ability to lower both

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[2592] *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).

[2593] 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 314.

[2594] *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).

[2595] *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).

serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population and do not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. As discussed above in Section V.E.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[2596] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[2597]

The proposed combination does not render the independent claim of the '677 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2598]

The analysis of the independent claim of the '677 patent is incorporated into all asserted claims that depend from this Claim.

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

[2596] Takaku at ICOSAPENT_DFNDT00006897.

[2597] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[2598] *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").

Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[2599]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.E.3.c.1.a.ii.a.iii is incorporated herein by reference. A person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[2600] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is

[2599] Defendants' Joint Invalidity Contentions at 314.

[2600] 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.

administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[2601] However, one of ordinary skill in the art knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[2602] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2603] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[2604] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

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[2601] Maki at 195.

[2602] 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.").

[2603] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2604] Defendants' Joint Invalidity Contentions at 314.

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

Indeed, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[2605]	-20%	+45%
Lovaza/Omacor[2606]	-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

[2605] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2606] Chan 2002 I at 2381 (Table 3).

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."[2607] 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.[2608] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not."[2609] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[2610] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with other saturated and polyunsaturated fatty acids.[2611] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[2612] Kelley does not show that

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[2607] Defendants' Joint Invalidity Contentions at 314-15.

[2608] 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.

[2609] Defendants' Joint Invalidity Contentions at 319.

[2610] The discussion related to Leigh-Firbank in Section V.A.3.c.1.a.i.a.iii is incorporated herein by reference.

[2611] The discussion related to Kelley in Section V.A.3.c.1.a.iii.a.ii is incorporated herein by reference.

[2612] *See* Mori 2006 at 96.

DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[2613] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[2614] Finally, Theobald also does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid. Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[2615]Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[2616] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after

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[2613] Kelley at 329.

[2614] 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.")

[2615] *See* Mori 2006 at 96.

[2616] Defendants' Joint Invalidity Contentions at 314.

EPA supplementation."[2617] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA," the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been well documented.[2618] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[2619] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[2620] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[2621]

[2617] Mori 2000 at 1092.

[2618] 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.

[2619] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[2620] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[2621] Harris 2008 at 13.

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA-E of WO '118."[2622] As discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[2623]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that DHA is *more* cardioprotective than EPA.[2624] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[2625] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[2626] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[2627] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA

[2622] Defendants' Joint Invalidity Contentions at 315.

[2623] 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").

[2624] Harris 2007 at 8.

[2625] *Id.*

[2626] 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.").

[2627] *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 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.").

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

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[2628] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[2629]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[2630] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[2631] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with

[2628] Defendants' Joint Invalidity Contentions at 316-17.

[2629] Defendants' Joint Invalidity Contentions at 317.

[2630] *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.").

[2631] Nakamura, Matsuzawa, and Takaku.

triglyceride levels > 500 mg/dL."[2632],[2633] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one patient had a baseline TG level > 500 mg/dL.[2634] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[2635] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[2636] Based on this disclosure, only one patient definitively had a baseline TG level $\geq$ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[2637] In Takaku, three patients had baseline TG levels above 500 mg/dL.[2638] However, the mean baseline TG level for all patients was 245 mg/dL.[2639] Indeed, the mean baseline TG level of the patients in all three

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[2632] Defendants' Joint Invalidity Contentions at 316.

[2633] 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.

[2634] Nakamura at 23, Table 1.

[2635] Nakamura at 23, Tables 1 and 2.

[2636] *Id.* at 23.

[2637] *Id.* at 10.

[2638] Takaku at ICOSAPENT_DFNDTS00006895.

[2639] Takaku at ICOSAPENT_DFNDTS00006875.

studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[2640] Defendants have failed to identify all of the claimed elements and fail to provide motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[2641] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[2642] In fact, Defendants acknowledge in their Joint Invalidity Contentions that

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[2640] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

[2641] Defendants' Joint Invalidity Contentions at 317.

[2642] Mori 2006 at 98.

"DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[2643] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[2644] Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG … that was achieved in six weeks of treatment," citing Mori 2000.[2645] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[2646] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,

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[2643] Defendants' Joint Invalidity Contentions at 321.

[2644] 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 grater with DHA supplementation than EPA supplementation).

[2645] Defendants' Joint Invalidity Contentions at 317.

[2646] Defendants' Joint Invalidity Contentions at 317.

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

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[2647] Therefore, a person of ordinary skill would not have been motivated to administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito treated subjects having baseline triglyceride levels greater than 500 mg/dl."[2648] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

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

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[2647] *See* Section III.

[2648] Defendants' Joint Invalidity Contentions at 317-18.

reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy."[2649] Defendants first support this argument by asserting that a person of ordinary skill in the art would have known that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition,[2650] however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[2651]

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

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[2652] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that

[2649] Defendants' Joint Invalidity Contentions at 319.

[2650] Defendants' Joint Invalidity Contentions at 319.

[2651] *See* Section IV.

[2652] Defendants' Joint Invalidity Contentions at 321.

the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[2653]

Defendants rely on Kelley and the Lovaza label to argue that "one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in LDL-C with DHA."[2654] However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[2655] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[2656] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not*

[2653] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese 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.

[2654] Defendants' Joint Invalidity Contentions at 321.

[2655] 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").

[2656] Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

reduce Apo-B[2657] (which is a reflection of total atherogenic lipoproteins)[2658] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

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

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

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[2659] Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo."[2660] However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of reducing triglycerides in a subject having very-high triglyceride levels by administering purified

[2657] *see* Section V.O.

[2658] *see* Section III.

[2659] Defendants' Joint Invalidity Contentions at 314.

[2660] Defendants' Joint Invalidity Contentions at 318.

EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore, Defendants fail to provide a reasonable expectation of success for the claimed invention.

Defendants further argue, that "because it was known that DHA and EPA were comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition with a reasonable expectation of success that such administration would result in reducing triglycerides while avoiding an increase in LDL."[2661] Defendants argument is without any basis. To the contrary, because a person of ordinary skill in the art would have understood DHA and EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no explanation and cite to no article to support their argument that the similar effects on TG levels is a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected *both* EPA and DHA, whether administered alone or in combination, would cause an increase in LDL-C when administered to the very high TG patient population.

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but

[2661] Defendants' Joint Invalidity Contentions at 322.

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[2662]	-20%	+45%
Lovaza/Omacor[2663]	-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 using EPA.

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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 '677 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

[2662] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2663] Chan 2002 I at 2381 (Table 3).

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.

(2) Dependent Claims

(a) Defendants Have Not Shown that Claims 2 and 3 of the '677 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.E.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 Claims 2 and 3.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claims 2 and 3. 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 combined to teach the administration of the claimed EPA to very high TG patients.[2664] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2665] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2666]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[2667]

[2664] *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").

[2665] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2666] *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").

[2667] *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

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[2668] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(b) Defendants Have Not Shown that Claim 4 of the '677 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.E.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 4.

Defendants contend that it would be obvious that a person receiving the claimed EPA compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) 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 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)).

[2668] *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.")

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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[2669] Defendants merely demonstrate that the element was purported known in the prior art without explaining how it can be combined with other elements.[2670] As such, Defendants discuss the claim element in isolation, and fail to address the claimed invention as a whole.[2671] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2672] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2673]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Further, Defendants do not

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[2669] *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").

[2670] *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").

[2671] *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").

[2672] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2673] *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").

discuss at all whether a person of ordinary skill would have been motivated to combine the elements, other than stating that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would have been motivated to combine the elements to achieve the claimed invention.[2674]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[2675] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

[2674] *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)).

[2675] *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.")

(c) Defendants Have Not Shown that Claim 5 of the '677 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.E.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 5.

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.[2676] 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.

[2676] *Id.*

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be combined.[2677] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[2678] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each prior art reference as a whole.[2679] Each reference must be evaluated for all that it teaches. Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2680]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed methods of treatment, without providing a reason that would have prompted a person of ordinary skill to combine the elements.[2681] Such a naked assertion does not show why a person of

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[2677] *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").

[2678] *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").

[2679] *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).

[2680] *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").

[2681] *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

ordinary skill would have been motivated to treat the recited patient population using the claimed methods of treatment.[2682]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[2683] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(d) Defendants Have Not Shown that Claims 6 and 7 of the '677 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.E.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 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)

[2682] *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)).

[2683] *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.")

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[2684] 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 further contend, without support, that a person of ordinary skill would "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude, without support, that it would have been obvious to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing triglycerides while

[2684] 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.

avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) 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 3) 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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[2685] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[2686] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2687] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2688]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those

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[2685] *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").

[2686] *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").

[2687] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2688] *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").

references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[2689] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[2690] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[2691] The mere fact that elements

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[2689] *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)).

[2690] 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).

[2691] *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).

are capable of being physically combined does not establish reasonable expectation of success.[2692]

(e) Defendants Have Not Shown that Claim 8 of the '677 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.E.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 8.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[2693] Defendants contend, without providing any support, that it would be obvious to one of skill in the art to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. 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

[2692] *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.").

[2693] *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").

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 combined to teach the administration of the claimed EPA to very high TG patients.[2694] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2695] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2696]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment would have been obvious but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[2697]

[2694] *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").

[2695] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2696] *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").

[2697] *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)).

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[2698] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

Beyond their laundry list of citations, Defendants rely on only one reference in their invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that "it was known that Apo-B is a component of LDL-C." Defendants cite to no passage or page of Theobald in connection with that argument and no support for their argument that Theobald makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all atherogenic lipoproteins.[2699]

Defendants then make the unsupported assertion that "one of ordinary skill in the art would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL syntheses." They are incorrect. Neither Defendants' characterization of Theobald nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render this claim obvious. Defendants' assertion that EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with respect to this claim or Apo-B levels.

[2698] *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.")

[2699] 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 *Crypthecodinium 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:[2700]

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

	DHA		Placebo		
	Before treatment	After treatment	Before treatment	After treatment	Treatment effect[1]
Total cholesterol (mmol/L)	5.15 ± 0.145[2]	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42)[3]
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)[4]
HDL cholesterol (mmol/L)[5]	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)[6]	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	−0.18 (−0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)[7]
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)[3]
Weight (kg)[8]	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (−0.85, 0.24)

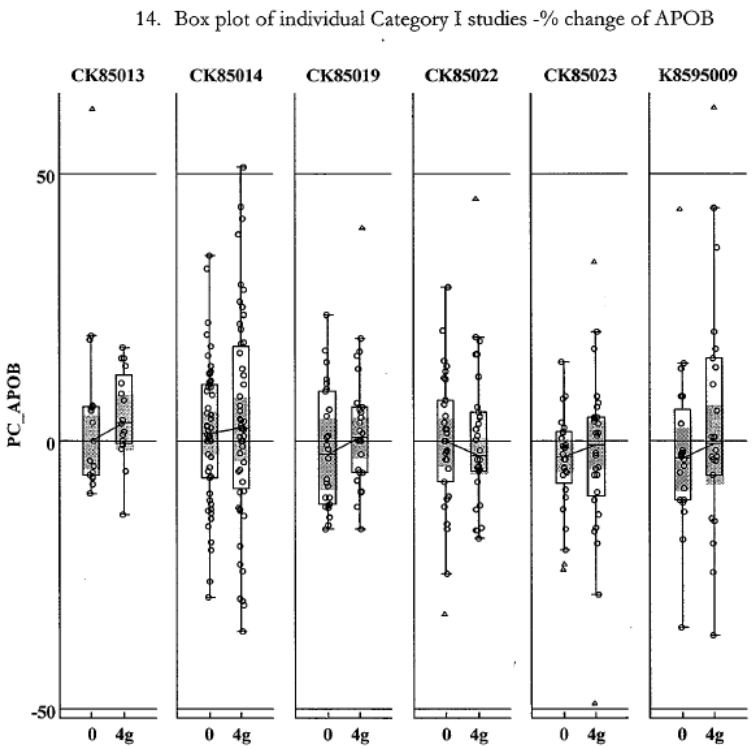
[1] Mean difference between active treatment and placebo; 95% CI in parentheses.
[2] $\bar{x}$ ± SEM (all such values); $n = 38$.
[3,4,7] Paired t test: [3] $P = 0.04$, [4] $P = 0.004$, [7] $P = 0.03$.
[5] HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.
[6] $n = 37$; data were log transformed before analysis by paired t test.
[8] Weight increased over the entire study period. Significant order × 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

[2700] Theobald at 561, table 3.

Apo-B levels in patients with very high TG levels.[2701] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[2702]



In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[2703] 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.[2704]

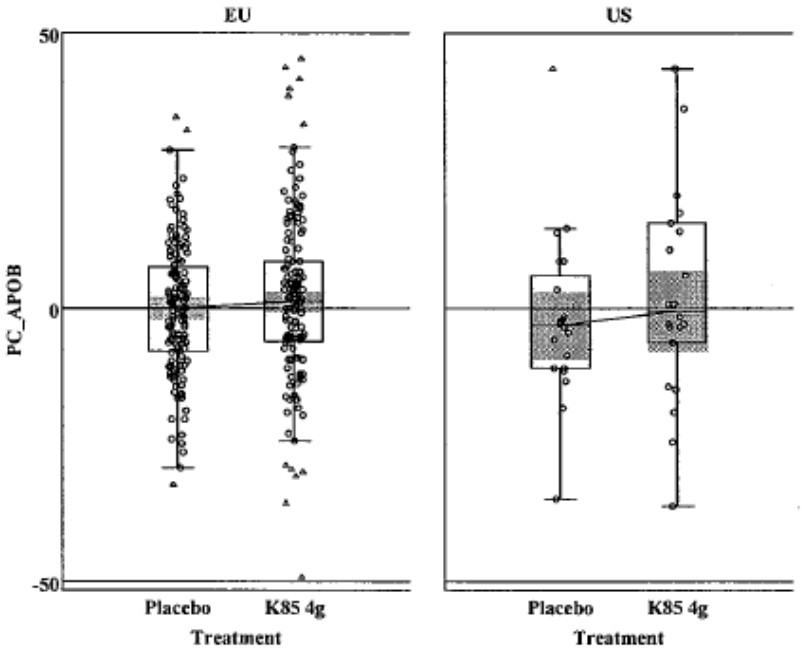
[2701] May 8, 2012 Bays Declaration.

[2702] Lovaza Approval Package at Table 14.

[2703] The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

[2704] 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.[2705] 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

[2705] *See* Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

those references, also reflecting a lack of motivation and no reasonable expectation of success.[2706]

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[2707] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[2708] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

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

(f) Defendants Have Not Shown that Claim 9 of the '677 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.E.3. Because Defendants have not shown the obviousness of the Independent Claim

[2706] Defendants' Contentions at 236.

[2707] ATP-III at 3170; Bays 2008 I at 395.

[2708] Kwiterovich in Kwiterovich at 4.

by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 9.

Defendants contend that it would have been obvious to use the claimed composition to reduce VLDL-C levels, and that the claimed VLDL-C reduction represents therapeutic efficacy, citing a laundry list of references without explaining how each reference relates to the claimed invention.[2709] 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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[2710] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[2711] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a

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[2709] *Id.*

[2710] *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").

[2711] *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").

whole. Each reference, however, must be evaluated for all that it teaches.[2712] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2713]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[2714] As such, Defendants fail to demonstrate that there was no motivation to combine the references to achieve the claimed invention.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that a person of ordinary skill would naturally seek to reduce VLDL-C levels to a therapeutic level, without providing a support other than simply identifying prior art references that purportedly disclose disparate elements.[2715] The mere fact that elements are capable of being physically combined

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[2712] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2713] *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").

[2714] *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)).

[2715] *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).

does not establish reasonable expectation of success.[2716] What is more, Defendants do not even discuss the reasonable expectation of reducing VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of reducing VLDL-C levels using the claimed methods.

4. The '677 Patent is Not Invalid Under § 112

a) Defendants Have Not Demonstrated that the Claims of the '677 Patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[2717] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the art about the scope of the invention" in light of the specification and the prosecution history.[2718] The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[2719]

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course,

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[2716] *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.").

[2717] 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 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.

[2718] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

[2719] *Id.* at 2129.

these terms are routinely used in patent claims, and are not *per se* indefinite.[2720] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[2721] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[2722] Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

Defendants further allege that the terms "4g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate" are indefinite. They contend that, because there is no indication of how much of the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[2723] In light of the

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[2720] *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) ("Claim language employing terms of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the context of the invention."); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir. 2003) ("The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification.") (discussing the term "about"); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) ("It is well established that when the term 'substantially' serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite.").

[2721] *See, e.g.*, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim 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).

[2722] *See generally* the '677 patent and its prosecution history.

[2723] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. 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,

specification and prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[2724] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants also allege that it is impossible to ascertain the metes and bounds of "compared to placebo control." A person of ordinary skill, however, would understand the metes and bounds of the term in light of the specification and the prosecution history.[2725] Moreover, the method of comparing a subject to a placebo control, such as a placebo controlled, randomized, double blind study, would have been known to a person of ordinary skill at the time of the invention. Therefore, the term does not render the claims indefinite.

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent."[2726] Plaintiffs assert that Defendants' ANDA products will be used

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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").

[2724] *See generally* the '677 patent and its prosecution history.

[2725] *See generally* the '677 patent and its prosecution history.

[2726] 35 U.S.C. § 271(c) (emphasis added).

in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '677 patent claims are not indefinite for improperly mixing methods and formulations.

b) Defendants Have Not Demonstrated that the Claims of the '677 Patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" to a skilled artisan that the applicant "invented" or "had possession" of the claimed subject matter when the application was filed.[2727] Support need not be literal[2728]—it may be implicit[2729] or inherent[2730] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[2731]

Defendants make three arguments regarding the written description requirement. First, Defendants contend that elements reciting the baseline TG levels of the asserted claims lack written description. This is incorrect. The specification of asserted patents literally discloses the claimed invention.[2732] Moreover, the recited baseline TG levels of the claimed invention appear

[2727] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[2728] *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).

[2729] *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.

[2730] *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

[2731] *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.

[2732] *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."); *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.").

in the original claims of the application to which the asserted patent claims priority. Thus, there is a strong presumption that the claimed invention is adequately described.[2733] Defendants do not and cannot rebut this presumption. Specifically, the patient population is originally claimed as "a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl."[2734] The asserted claims recite the same patient population. Defendants do not contend that the patient population of the asserted claims is not literally described by the specification and in the original claims of the application to which the asserted patent claims priority. In fact, the specification and the provisional patent application claims at the time of filing describe these limitations.[2735] Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the dosages and quantities of the claimed methods.[2736] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the

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[2733] *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").

[2734] *See* U.S. Application No. 12/702,889.

[2735] '677 patent at 13:29-34; 14:29-51; U.S. Provisional Application No. 61/151,291.

[2736] *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."); *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.").

claimed invention is adequately described.[2737] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[2738] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants appear to suggest, although they have not specifically contended, that "a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against" placebo control. The specification demonstrates that the applicants were in possession of the claimed inventions. For example, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a comparison of a subject or a population against placebo control.

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[2739] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification

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[2737] *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").

[2738] *See* U.S. Provisional Application No. 61/151,291.

[2739] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[2740] Written description requires only that the specification reasonably conveys that the applicant had possession of the claimed subject matter when the application was filed. Therefore, whether the claims are obvious has no bearing on the adequacy of written description.

c) Defendants Have Not Demonstrated that the Claims of the '677 Patent Are Invalid for Lack of Enablement

The first paragraph of 35 U.S.C. § 112 requires that the specification "enable any person skilled in the art . . . to make and use [the claimed invention]." A claim is not enabled if it would require undue experimentation for a person of ordinary skill to make or use the invention. Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or

[2740] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is 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 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.").

unpredictability of the art, and the breadth of the claims.[2741] The enablement requirement is separate and distinct from the written description requirement,[2742] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[2743]

Defendants make two specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary skill would be able to determine the amounts of the components in the pharmaceutical composition without any experimentation, much less undue experimentation.

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to

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[2741] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[2742] *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[2743] MPEP § 2164.

patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[2744] Therefore, the claims are not invalid for lack of enablement.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '677 patent's specification enables a person of ordinary skill to obtain the claimed limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.E.3. Furthermore, Plaintiffs have initiated human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its claimed methods.[2745, 2746] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

F. **The '446 Patent**

1. The '446 Patent Claims Eligible Subject Matter Under § 101

Defendants' allegation that the asserted claims of the '446 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

[2744] *See* VASCEPA Prescribing Information at Table 2.

[2745] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical 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.").

[2746] *See* May 16, 2011 Bays Declaration at Appendix B.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[2747] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '446 patent does not meet this requirement and thwarts the purpose of the Rules.[2748]

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical phenomenon, or abstract idea.[2749] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[2750]

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '446 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and] conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[2751] However, the claims merely recited this natural law without

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[2747] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[2748] Nor does the preceding paragraph, which provides only a purported summary of the claims of the '446 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).

[2749] *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) ("First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts.").

[2750] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

[2751] *Mayo*, 132 S. Ct. at 1294.

reciting any novel application of it.[2752] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[2753] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[2754]

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions make clear that EPA of the requisite purity and characteristics is not found in nature.[2755] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their natural state are patent-eligible.[2756] Moreover, Defendants' assertions are immaterial to a Section 101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[2757]

[2752] *Id.* at 1301.

[2753] *Id.*

[2754] *Id.* at 1302 (contrasting the patent-ineligible claims of that case to "a typical patent on a new drug or a new way 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).

[2755] *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).

[2756] *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).

[2757] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[2758] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[2759] To say that the claims of the '446 patent claim a law of nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to underlying principles of nature" that would "make all inventions unpatentable."[2760] Indeed, even those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[2761]

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '446 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to

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[2758] *See* Defendants' Joint Invalidity Contentions at 429.

[2759] See *CellzDirect*, 827 F.3d at 1048-49 ("The [asserted] claims are like thousands of others that recite processes 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).").

[2760] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

[2761] *See Mayo*, 132 S. Ct. at 1034 ("Prometheus, supported by several *amici*, argues that a principle of law denying patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research.").

foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[2762] As discussed above, the asserted claims of the '446 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[2763]

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In addition, as discussed above, the asserted claims are not merely a naturally-occurring phenomena, and thus satisfy the requirements of § 101.

2. The Asserted Claims of the '446 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[2764] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.[2765] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[2766] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[2767] In addition, public

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[2762] *See Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

[2763] *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 "just one step in the whole process" claimed by the invention).

[2764] *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

[2765] *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).

[2766] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[2767] *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).

"possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[2768] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[2769] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[2770]

Defendants assert that Claims 1-11 of the '446 Patent are anticipated by the WO '118 reference.[2771]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference into Exhibit F, and vice-versa. WO '118 does not anticipate the claims of the '446 patent because it does not describe, properly arrange, or enable the '446 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '446 Patent

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

It is well established that, for a prior art reference to anticipate, "every element of the

[2768] *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).

[2769] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[2770] *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).

[2771] 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.

claimed invention must be identically shown in a single reference."[2772] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[2773] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '446 Patent: *to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[2774] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claim of the '446 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable

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[2772] *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).

[2773] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

[2774] Defendants' Invalidity Contentions at 202-204.

weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[2775] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[2776] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[2777] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claim every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[2778] Rambjor is a clinical study which administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

Therefore, WO '118 cannot anticipate the independent claim of the '446 patent. Because the dependent claims include all of the claim elements of the independent claim, WO' 118 cannot anticipate any of the dependent claims as well.

[2775] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[2776] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[2777] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[2778] *See, e.g.*, Rambjor.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[2779] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[2780]

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

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[2781] The recitation of a "method of

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[2779] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

[2780] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

[2781] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer 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").

reducing triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[2782] Thus, the entire preamble in the independent claim of the '446 must contain patentable weight.

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

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina."[2783] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[2784] WO '118 does not

[2782] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

[2783] WO '118 at 12.

[2784] *Id.*

expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claim.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of the reference.[2785] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

There is no evidence in that subject as described in the claims were ever treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of the subject as described in the claims. It does not. Defendants' argument rests on the definition in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL." WO '118's definition is not tied to a specific subject and there are no working examples, data or other reference in WO '118 indicating that any subject with fasting TG levels of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as evidence that a "person of ordinary skill in the art would have understood that the term 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable and then merely provides examples of commercially available "soft capsules," such as Omacor. The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be

[2785] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[2786] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claim every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '446 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[2787] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[2788] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

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[2786] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[2787] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[2788] *Atofina*, 441 F.3d at 1000.

compared to the patent's claimed range of 0.1 to 5.0 percent.[2789] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[2790] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[2791] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[2792] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),

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[2789] *Id.*

[2790] *Id.*

[2791] *See* Section III.

[2792] *Id.*

and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[2793] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[2794] Accordingly, in these populations, physicians focused on lowering LDL-C.[2795] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary treatment goal.[2796] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claim of the '446 Patent.

[2793] ATP III at 3335; *See also* Section III.

[2794] *Id.*

[2795] *Id.*

[2796] *Id.*

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

WO '118 further does not anticipate the claims of the '446 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '446 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more 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 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic

range of 330 to 450 °C,"[2797] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[2798] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[2799] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '446 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '446 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '446 patent and cannot anticipate the independent claim of the '446 Patent.

WO '118 further does not anticipate the claims of the '446 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[2800] Therefore, WO '118 discloses

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[2797] *Atofina*, 441 F.3d at 1000.

[2798] *Id.*

[2799] *Id.*

[2800] WO '118 at 22.

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

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[2801] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[2802] and therefore failed to anticipate the claimed range.[2803] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[2804] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[2805]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '446 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '446 patent. Therefore, WO '118's broad

[2801] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[2802] *Atofina*, 441 F.3d at 1000.

[2803] *Atofina*, 441 F.3d at 1000.

[2804] *Id.*

[2805] *Id.*

disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claim of the '446 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[2806] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '446 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between. There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claim of the '446 patent.

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

[2806] WO '118 at 22.

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

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

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

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

inherently anticipate as a matter of law."[2807] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[2808] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[2809] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

3. The Claims of the '446 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '446 Patent obvious.[2810] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '446 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of

[2807] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[2808] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[2809] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[2810] Defendants' Joint Invalidity Contentions at 13-25.

the '446 Patent itself to guide its combination of references.[2811] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[2812]

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

- 1) ". . .the asserted claims of the '446 patent would have been obvious over 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."

- 2) ". . .the asserted claims of the '446 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified 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."

- 3) ". . .the asserted claims of the '446 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '446 patent would have been obvious over WO '118 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."

[2811] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention 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))).

[2812] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, 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 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.

- 5) ". . . the asserted claims of the '446 patent are obvious over 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."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[2813] 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.[2814]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[2815] Indeed, any teaching in the art that points away from the claimed invention must be considered.[2816] A reference teaches away if a person of ordinary skill, upon reading 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.[2817] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[2818]

[2813] 35 U.S.C. § 103(a).

[2814] *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).

[2815] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2816] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

[2817] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[2818] *Id*.

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[2819] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[2820] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[2821]

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[2822] "[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."[2823] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[2824]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[2825] or to modify a prior art reference in a way that

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[2819] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[2820] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[2821] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

[2822] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[2823] *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))

[2824] *KSR*, 550 U.S. at 418-419.

[2825] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

"would destroy the fundamental characteristics of that reference."[2826] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[2827] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[2828] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[2829]

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[2830] and "a reasonable expectation of success."[2831]

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[2832] This protects against the use of hindsight to pick through the prior art

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[2826] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[2827] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[2828] *Id*. at 88.

[2829] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

[2830] *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).

[2831] *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).

[2832] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; 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).

based solely on structural similarity to the claimed compound.[2833] Any assertion of an "apparent reason" must find a basis in the factual record.[2834]

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[2835] including those discovered after the patent was filed or even issued.[2836] "The basic principle behind this rule is straight-forward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[2837] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[2838]

[2833] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (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).

[2834] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[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*, 619 F.3d at 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 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").

[2835] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [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.").

[2836] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

[2837] *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.").

[2838] *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

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[2839] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[2840] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[2841] These factual inquiries "guard against slipping into use of hindsight,"[2842] and "may often be the most probative and cogent evidence of nonobviousness."[2843]

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[2844]

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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.'").

[2839] *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).

[2840] *Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1569 (Fed. Cir. 1987).

[2841] *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.

[2842] *Graham*, 383 U.S. at 36.

[2843] *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)).

[2844] *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.").

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

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying degrees of purity, in a wide range of doses and administration periods, to subjects who have baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[2845] Inconsistency in dosages and administration periods and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[2846] Defendants

[2845] Mori 2006 at 96.

[2846] Defendants' Joint Invalidity Contentions at 440 (*see* FN 76).

mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[2847] In addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[2848] Clinically, the authoritative guidance to physicians

[2847] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 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).

[2848] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[2849]

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

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[2850] The fibrate, Tricor (fenofibrate), for example, decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[2851]

[2849] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

[2850] *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).

[2851] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[2852] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[2853] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[2854] Similar results were seen with the administration of Lopid (gemfibrozil).[2855] The differing effects of fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	**Mean Baseline TG Value**	**TG**	**LDL-C**	**HDL-C**	**Total-C**
Tricor (fenofibrate)[2856]	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*

[2852] *Id.*

[2853] *Id. See also*, Trilipix Label at 27.

[2854] *Id. See also*, Trilipix Label at 27.

[2855] *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).

[2856] 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.[2857] It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.[2858] 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%.[2859] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[2860]

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

[2857] Chan 2002 I at 2379-81.

[2858] *Id.; See also*, Westphal at 918.

[2859] *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

[2860] *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 [cholesteryl 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.)"

levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[2861] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[2862] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '446 patent are inherent to the compound when administered to a human subject."[2863] Inherency may not supply a missing

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[2861] Bays May 16, 2011 Decl., ¶ 11 (noting the "general knowledge in the art that omega-3 fatty acids as a class increase LDL-C" in very-high TG patients); McKenney 2007, at 724 ("Because of the increase in LDL levels 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.").

[2862] Bays 2008 I at 400-402.

[2863] Defendants' Joint Invalidity Contentions at 441.

claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[2864] Obviousness is based on what is *known* in the art at the time of the invention.[2865] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[2866] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

Defendants argue that the claims of the '446 patent which contain "a limiting clause, such as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively recited and therefore are not elements.[2867] This is incorrect. "There is nothing inherently wrong with defining some part of an invention in functional terms."[2868] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[2869] The claim term "to effect" acts as a positive limitation if the term represents

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[2864] *See, e.g.*, *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) ("A party must . . . 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).

[2865] *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.").

[2866] *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

[2867] Defendants' Joint Invalidity Contentions at 441.

[2868] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

[2869] Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

"unexpected and improved effects of administration of the claimed compound."[2870] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

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

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

(1) WO '118

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '446 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited

[2870] 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).

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

With respect to Claim 1 of the ‘446 Patent (and therefore all asserted claims), WO ‘118 does not disclose or suggest a subject with the recited very high TG level. WO ‘118 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or dosage. WO ‘118 further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(2) WO ’900

WO ‘900 describes methods for obtaining EPA-rich compositions.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO ‘900 disclose or suggest elements of the ‘446 Claims. The cited portions of WO ‘900 do not disclose or suggest these elements at least because they do not disclose or suggest administration

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

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. WO '900 further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(3) Contacos

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '446 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Contacos further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

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

administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(4) Grimsgaard

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of the '446 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG level. Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited administration period. Grimsgaard further does not disclose or suggest a method to effect the recited TG

reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-10, this reference fails to disclose or suggest the recited capsule dosage.

(5) Hayashi

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

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '446 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the

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

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Hayashi further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(6) Katayama

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '446 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest

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

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Katayama further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(7) Leigh-Firbank

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '446 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

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

reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(8) Lovaza PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '446 Claims. The cited portions of the Lovaza PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Lovaza PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claims 4 and 5, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed

pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(9) Maki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '446 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Maki further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Maki further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(10) Matsuzawa

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Matsuzawa disclose or suggest elements of the '446 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Matsuzawa further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Matsuzawa does not disclose or suggest a subject with the recited very high TG level. Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Matsuzawa further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(11) Mori 2000

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of the '446 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited

portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. Mori 2000 further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(12) Mori 2006

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '446 Claims. The cited portions of Mori 2006 do not

disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. The cited portions of Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. Mori 2006 further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '446 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '446 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not

disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Nozaki further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(14) Omacor PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '446 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Omacor PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or administration period. The cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claims 4 and 5, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG without substantially increasing LDL-C based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '446 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited dosage. The cited portions of Satoh further do not disclose or suggest a method to

effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage. Satoh further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(16) Shinozaki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '446 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels.

The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage. Shinozaki further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '446 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

With respect to Claim 1 of the '446 Patent (and therefore all asserted claims), Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Takaku further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to placebo control.

Further, with respect to Claim 2, this reference fails to disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claim 3, this reference fails to disclose or suggest the subject with the recited baseline lipid levels. With respect to Claims 4 and 5, this reference fails to disclose or suggest the recited reduction in TG without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 6, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG levels based on a comparison to placebo control. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction

in VLDL-C in the subject with the claimed TG levels based on a comparison to placebo control. With regards to claims 8-11, this reference fails to disclose or suggest the recited capsule dosage.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '446 Patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '446 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 1 (and therefore Claims 2-11): *administering the claimed pharmaceutical composition to the recited subject to effect a reduction in triglycerides without substantially increasing LDL-C based upon a comparison to placebo control*. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '446 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '446 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claim of the '446 Patent Would Have Been Obvious

(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."[2871] 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.[2872, 2873] Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent

[2871] Defendants' Joint Invalidity Contentions at 435.

[2872] 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, Mataki, 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 Invalidity Contentions at 434-35.

[2873] 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 Invalidity Contentions at 433.

reason" to combine must find a basis in the factual record.[2874] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2875] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2876] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,

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[2874] *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).

[2875] *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").

[2876] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claim of the '446 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2877]

The analysis of the independent claim of the '446 Patent is incorporated into all asserted claims that depend from this Claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '446 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies

[2877] *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").

were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.[2878] As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-high or high TG patients, was expected. At the priority date of the '446 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[2879] This is an incorrect

[2878] *See* Grimsgaard at 652 (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.)

[2879] Defendants' Joint Invalidity Contentions at 435-36.

characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2880] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference

[2880] Defendants' Joint Invalidity Contentions at 435-136.

disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[2881] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[2882]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2883] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[2884] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[2885] Katayama does not disclose *any* LDL-C related

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[2881] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI_2 and PGI_3 Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[2882] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[2883] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2884] Defendants' Joint Invalidity Contentions at 436.

[2885] Katayama at 2.

data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[2886] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[2887] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[2888] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

[2886] *Id.* at 16.

[2887] Defendants' Joint Invalidity Contentions at 436.

[2888] Matsuzawa at 7 and 19.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[2889] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[2890] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[2891] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

[2889] *Id.* at 23.

[2890] *Id.* at 10.

[2891] *Id.* at 11.

triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[2892] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2893] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '446 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '446 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain

[2892] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

[2893] *See, e.g.*, Rambjor.

why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[2894] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[2894] Nozaki at 256.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[2895] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2896] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

[2895] Hayashi at 26, Table I.

[2896] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

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

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2897] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)

[2897] Defendants' Joint Invalidity Contentions at 438.

would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[2898] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[2899] and DHA

[2898] Mori 2006 at 96.

[2899] Leigh-Firbank at 440.

is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[2900] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "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."[2901] Although teaching away is fact-dependent, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[2902]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[2903] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[2904] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may

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[2900] *See, e.g.* Grimsgaard at 654.

[2901] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[2902] *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.").

[2903] Mori 2000 at 1092.

[2904] Mori 2000 at 1088.

be favorable."[2905] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2906] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '446 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or

[2905] Mori 2000 at 1092.

[2906] *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 '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."[2907] 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.[2908] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2909] Defendants' contentions are no more than an assertion that certain

[2907] Defendants' Joint Invalidity Contentions at 435.

[2908] *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).

[2909] *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").

claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2910] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claim of the '446 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2911]

The analysis of the independent claim of the '446 Patent is incorporated into all asserted claims that depend from this Claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to

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[2910] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2911] *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").

Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '446 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.F.3.c.1.a.i.a.i, incorporated herein by reference, Katayama and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[2912] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

[2912] Defendants' Joint Invalidity Contentions at 438-39.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[2913] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[2914] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in 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."[2915] 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

[2913] Defendants state in their Joint Invalidity 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).

[2914] Grimsgaard at 654.

[2915] Defendants' Joint Invalidity 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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[5]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[2916] 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."[2917] 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

[2916] Grimsgaard at 657.

[2917] Grimsgaard at 654.

it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard 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." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[2918] A person of ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[2919] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[2920] based on long-term administration.[2921]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a

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[2918] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to 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.

[2919] Defendants' Joint Invalidity Contentions at 436.

[2920] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[2921] Takaku at ICOSAPENT_DFNDT00006834.

conclusion "only from the results of the present study."[2922] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[2923]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[2924] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[2925] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[2926] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other

[2922] Takaku at ICOSAPENT_DFNDT00006897.

[2923] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[2924] Takaku at ICOSAPENT_DFNDT00006884.

[2925] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[2926] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

times.[2927] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[2928]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[2929] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2930] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '446 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

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[2927] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[2928] Takaku at ICOSAPENT_DFNDT00006897.

[2929] Takaku at ICOSAPENT_DFNDT00006897.

[2930] *See, e.g.*, Rambjor.

claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[2931] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person

[2931] Nozaki at 256.

of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[2932] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2933] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Further, Defendants have failed to offer a purported combination of references as part of their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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[2932] Hayashi at 26, Table I.

[2933] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

motivation to combine Nozaki and Hayashi with the other references of their purported obviousness combinations. Therefore, Defendants should be precluded from relying on these references.

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2934] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or Maki —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

[2934] Defendants' Joint Invalidity Contentions at 438.

not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[2935] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[2936] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with below-average levels of HDL-C levels.[2937] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated, monounsaturated and polyunsaturated fatty acids.[2938] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[2939] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have also contributed to the elevation in LDL cholesterol."[2940] Further, Maki admits that the

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[2935] Defendants' Joint Invalidity Contentions at 438-39.

[2936] Defendants' Joint Invalidity Contentions at 438.

[2937] Maki at 190.

[2938] Maki at 191.

[2939] Maki at 195.

[2940] 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).

"mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[2941] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Defendants mischaracterize the rise in LDL-C associated with the administration of omega-3 fatty acids as being a "negative effect" because they incorrectly focus on only the LDL-C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in LDL-C to be troublesome; Maki states that "the lack of increase in the total/HDL cholesterol ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level less worrisome."[2942] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[2943]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2944] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

[2941] Maki at 197.

[2942] Maki at 197.

[2943] Maki at 197.

[2944] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

(iii) The '446 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or in View of Satoh or Shinozaki in Further View of Contacos

With respect to the '446 Patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[2945] Defendants also present charts purporting to assert that an additional 60 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 60 separate references, they additionally do not suggest any identify 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.[2946] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2947] Defendants' contentions are no more than an assertion

[2945] Defendants' Joint Invalidity Contentions at 436.

[2946] *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).

[2947] *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").

that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2948] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference would cause a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels.

Defendants formulate an obviousness argument that relies on Contacos.[2949] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim

[2948] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2949] *Id.*

element, an "apparent reason" or motivation to combine the elements in the manner claimed,[2950] or "a reasonable expectation of success"[2951] of achieving the claimed invention.

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

The proposed combinations do not render the independent claim of the '446 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2952]

The analysis of the independent claim of the '446 Patent is incorporated into all asserted claims that depend from this Claim.

[2950] *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).

[2951] *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).

[2952] *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").

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '446 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

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

Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.F.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely confirms the safety of long term treatment of Epadel and its ability to lower both serum total 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 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when

compared to baseline, there was no significant effect when compared to placebo.[2953] Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2954] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C.

Further, Satoh was a small study conducted in only Japanese patients. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2955] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a

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[2953] Satoh at 145.

[2954] Defendants' Joint Invalidity Contentions at 436.

[2955] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2956] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[2957] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2958] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki and/or Contacos.

(ii) Geppert and/or Kelley Do Not Disclose Purported Knowledge that DHA was

[2956] Defendants' Joint Invalidity Contentions at 436.

[2957] Shinozaki at 107-109.

[2958] *See, e.g.*, Rambjor.

Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2959] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement do not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels, respectively. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or Kelley —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

Defendants rely on Geppert and/or Kelley to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[2960] Both Geppert and Kelley administer DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.

[2959] Defendants' Joint Invalidity Contentions at 438.

[2960] Defendants' Joint Invalidity Contentions at 436.

Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[2961] For example, Defendants' own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.[2962]

In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[2963] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA was the only component of fish oil to increase LDL-C. For example, there is no data comparing DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying explain the mechanism of LDL-C increase.[2964] A person of ordinary skill would have not expected that EPA and DHA would have different effects on LDL-C based on Geppert.

Defendants contend that Kelley shows that DHA was responsible for the increase in LDL-C.[2965] In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day

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[2961] *See* Mori 2006 at 96.

[2962] Maki at 197.

[2963] Geppert at 784.

[2964] *Id*.

[2965] Defendants' Joint Invalidity Contentions at 436.

of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[2966] Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in context with the other lipid effects reported in the study. Kelley states that:

> DHA supplementation may lower the risk of CVD by reducing plasma triacylglycerols; triaclyglycerol:HDL; the number of small, dense LDL particles; and mean diameter of VLDL particles. An increase was observed in fasting LDL cholesterol, but it is unlikely this increase is detrimental because no increase was observed in the overall number of LDL particles; actually, there was an 11% reduction that was statistically not significant. The reason LDL cholesterol increased despite no change in LDL particle number was that the LDL particles were made larger and hence more cholesterol rich by DHA treatment.[2967]

Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. 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."[2968] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with 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

[2966] Kelley at 329.

[2967] Kelley at 329

[2968] Kelley at 324, 332.

mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy, including administration of DHA. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

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

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2969] As is the case with Kelley, Defendants use hindsight to characterize a reference based on LDL-C levels alone without considering the other lipid effects studied, considered and reported.[2970] The isolated manner in which Defendants select such data points is not the approach that a person of ordinary skill would have taken at the time of the invention. Defendants' approach represents the use of impermissible hindsight bias. A person of ordinary skill would take into consideration the entire disclosure of a reference, including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a favorable effect in hypertriglyceridemic patients.

[2969] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[2970] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation 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.").

Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2971] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert and/or Kelley.

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

Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[2972] Fibrates were effective at

[2971] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2972] *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).

reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[2973] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[2974] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[2975] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

In any event, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[2976]	-20%	+45%
Lovaza/Omacor[2977]	-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

[2973] 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");

[2974] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[2975] *See Id.*, ¶ 17

[2976] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2977] Chan 2002 I at 2381 (Table 3).

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 the lack of motivation.

Defendants offer no "apparent reason" to administer EPA as claimed to patients with fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on Lovaza/Omacor as the starting point to "find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels."[2978] Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG reduction and the increased conversion of VLDL to LDL particles.[2979]

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[2980] A person of ordinary skill in the art understood that EPA and DHA

[2978] Defendants' Joint Invalidity Contentions at 437.

[2979] *See* Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that "[t]hese 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

[2980] 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")

had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[2981] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels the most in patients with the highest pretreatment TG levels.[2982] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-C was often offset by concurrent treatment with statins.[2983] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[2984]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[2985] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[2986]

[2981] 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)

[2982] *See* Bays 2008 Rx Omega-3 p. 402.

[2983] *See* Harris 2008 at 14, McKenney at 722.

[2984] McKenney at 722-23.

[2985] *See* Westphal at 918, Harris 1997 at 389.

[2986] *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 chancing 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

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[2987] Correspondingly, prescription omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[2988] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the number of small, dense LDL particles to larger LDL particles.[2989] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[2990] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not

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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)").

[2987] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

[2988] McKenney 2007 at 722 (*see* Fig. 1).

[2989] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[2990] Stalenhoef at 134.

only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[2991]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[2992] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[2993] (which is a reflection of total atherogenic lipoproteins) [2994] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

[2991] Harris 1997 at 389.

[2992] Defendants' Joint Invalidity Contentions at 437.

[2993] *see* Section V.O.

[2994] *see* Section III.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention. Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population, they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill would have understood these patient populations to be distinct with different impacts of lipid therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would not have considered the dosage modification suggested by defendants to be routine; Defendants' argument to the contrary represents hindsight bias.

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

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

Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing

triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by combining the references cited by defendants. For a particular combination of references, there must be a reasonable expectation that the combination will produce the claimed invention. In this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG levels.[2995] A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG patient population. As discussed in Section III and above, it was well known that TG-lowering 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[2996]	-20%	+45%
Lovaza/Omacor[2997]	-6%	+45%

[2995] As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to have the same TG lowering mechanism and would have further understood that the increase in LDL-C 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.

[2996] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[2997] Chan 2002 I at 2381 (Table 3).

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.[2998]

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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.[2999] Epadel was available for many years prior to the invention of the '446 patent, to patients with very-high TGs as a treatment. 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. 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

[2998] 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.

[2999] 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.

Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides.

Defendants argue that because Grimsgaard administered purified ethyl EPA to patients with borderline-high/high TG, it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.[3000] Defendants' contentions are no more than a demonstration that certain claim elements was known in the prior art and demonstrates impermissible hindsight reconstruction.[3001] As is reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA, 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.

[3000] Defendants' Joint Invalidity Contentions at 439-40.

[3001] *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.").

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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[5]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[5]	0.96 ± 0.13	0.04 ± 0.08[5]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

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

Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[3002] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[3003] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

Defendants argue that a person of ordinary skill at the time of the invention, based on studies in normal, borderline-high and high TG patients, knew that administration of DHA alone resulted in undesirable increased LDL-C levels while administration of EPA alone had little to no impact on LDL-C levels.[3004] However, that statement does not conform with what was known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor were both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

With the lack of any reasonable expectation of success, Defendants argue that their proposed combination amounts to a simple substitution of one known element for another, and that that these changes yield predictable results.[3005] Such an argument, however, represents pure and impermissible hindsight bias and further does not consider that reasons for which a person of

[3002] *See Sanofi*, 748 F.3d at 1360–61.

[3003] *See supra* Section III.

[3004] Defendants' Joint Invalidity Contentions at 439.

[3005] Defendants' Joint Invalidity Contentions at 440.

ordinary skill would not be motivated to combine these references and affirmatives ways in which the art taught away from these combinations.

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

(i) The '446 Patent is not Obvious Over WO '118 or WO '900, in Combination with the Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '446 Patent, Defendants present a combination of five references: "WO '118 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."[3006] Defendants also present charts arguing 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.[3007, 3008] Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent

[3006] Defendants' Joint Invalidity Contentions at 442.

[3007] Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, 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 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.

[3008] 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 Invalidity Contentions at 433-34.

reason" to combine must find a basis in the factual record.[3009] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3010] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3011] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[3012] Contrary to Defendants' assertion that WO '118 discloses

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[3009] *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) (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 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).

[3010] *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").

[3011] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3012] WO '118 at 9.

"the administration of 4 g of pure EPA with no DHA,"[3013] WO '118 fails to disclose the claimed subject with the specified very high TG levels (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[3014]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[3015] WO '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[3016]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[3017] WO '118 states that "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +

[3013] Defendants' Joint Invalidity Contentions at 442.

[3014] WO '118 at 22-23.

[3015] WO '118 at 8.

[3016] *See* Section III.

[3017] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[3018] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[3019] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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

WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[3020] Moreover, WO '900 does not teach the desired effect of EPA other than commenting generally that it "may promote health and ameliorate or even reverse the effects of a range of common diseases."[3021] It has no discussion, for example, on any TG-lowering effect of EPA. Although WO '900 identifies DHA as an "undesired molecule", it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than

[3018] WO '118 at 22-23.

[3019] WO '118 at 23.

[3020] *See, e.g.*, '900 Pub. at 16-17.

[3021] '900 Pub. at 5.

commenting generally that "the desired effects of EPA may be limited or reversed" by them.[3022] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claim of the '446 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3023]

The analysis of the independent claim of the '446 patent is incorporated into all asserted claims that depend from this Claim.

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[3024]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references,

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[3022] '900 Pub. at 39.

[3023] *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").

[3024] Defendants' Joint Invalidity Contentions at 443.

any assertion of an "apparent reason" to combine must find a basis in the factual record.[3025] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3026] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

Contrary to Defendants' assertion, Leigh-Firbank and Mori 2000 do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank and Mori 2000 in Section V.F.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation

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[3025] *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).

[3026] *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").

to combine with WO '118 or WO '900. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3027] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '446 Patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in View of Katayama, Matsuzawa and/or Takaku.

With respect to the '446 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."[3028] 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.

[3027] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[3028] Defendants' Joint Invalidity Contentions at 443.

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.[3029] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3030] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3031] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The discussion related to WO '118 and WO '900 in Section V.F.3.c.1.b.i is incorporated herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.F.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that "Grimsgaard and Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA." However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the

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[3029] *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).

[3030] *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").

[3031] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

very high TG patient population. Neither Grimsgaard nor Mori 2000 provides motivation to administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Grimsgaard or Mori 2000.

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[3032] 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.[3033] Defendants' assertions related to motivation are insufficient,[3034] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

[3032] Defendants' Joint Invalidity Contentions at 443.

[3033] *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).

[3034] 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 444.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[3035] or "a reasonable expectation of success"[3036] of achieving the claimed invention. Therefore, Defendants should be precluded from relying on this these references.

As discussed above in Section V.F.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population and do not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. As discussed above in Section V.F.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[3037] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in

[3035] *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).

[3036] *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).

[3037] Takaku at ICOSAPENT_DFNDT00006897.

Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[3038]

The proposed combination does not render the independent claim of the '446 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3039]

The analysis of the independent claim of the '446 patent is incorporated into all asserted claims that depend from this Claim.

(a) Grimsgaard, Mori 2000 and/or Maki Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[3040]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.F.3.c.1.a.ii.a.iii is incorporated herein by reference. A

[3038] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[3039] *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").

[3040] Defendants' Joint Invalidity Contentions at 443.

person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[3041] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[3042] However, one of ordinary skill in the art knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[3043] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or

[3041] 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.

[3042] Maki at 195.

[3043] 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.").

has little effect on LDL-C levels.[3044] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[3045] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides *without increasing LDL-C levels*.

Indeed, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients

[3044] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[3045] Defendants' Joint Invalidity Contentions at 444.

Fibrate[3046]	-20%	+45%
Lovaza/Omacor[3047]	-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."[3048] 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.[3049] Therefore, a person of ordinary skill would not have concluded that DHA increases

[3046] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3047] Chan 2002 I at 2381 (Table 3).

[3048] Defendants' Joint Invalidity Contentions at 444.

[3049] 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.

LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not."[3050] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[3051] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with other saturated and polyunsaturated fatty acids.[3052] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[3053] Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[3054] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[3055] Finally, Theobald also

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[3050] Defendants' Joint Invalidity Contentions at 449.

[3051] The discussion related to Leigh-Firbank in Section V.F.3.c.1.a.i.a.iii is incorporated herein by reference.

[3052] The discussion related to Kelley in Section V.F.3.c.1.a.iii.a.ii is incorporated herein by reference.

[3053] *See* Mori 2006 at 96.

[3054] Kelley at 329.

[3055] 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.")

does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid. Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[3056]Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[3057] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[3058] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,"

[3056] *See* Mori 2006 at 96.

[3057] Defendants' Joint Invalidity Contentions at 444.

[3058] Mori 2000 at 1092.

the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been well documented.[3059] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[3060] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[3061] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[3062]

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."[3063] As discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[3064]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that

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[3059] 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.

[3060] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[3061] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[3062] Harris 2008 at 13.

[3063] Defendants' Joint Invalidity Contentions at 445.

[3064] 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").

DHA is *more* cardioprotective than EPA.[3065] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[3066] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[3067] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[3068] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA *and* DHA were known to have cardioprotective effects, and there were studies suggesting DHA was *more* cardioprotective than EPA.

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[3069] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free,

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[3065] Harris 2007 at 8.

[3066] *Id.*

[3067] 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.").

[3068] *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 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.").

[3069] Defendants' Joint Invalidity Contentions at 446.

highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[3070]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[3071] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[3072] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG levels > 500 mg/dL."[3073],[3074] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one

[3070] Defendants' Joint Invalidity Contentions at 446.

[3071] *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.").

[3072] Nakamura, Matsuzawa, and Takaku.

[3073] Defendants' Joint Invalidity Contentions at 446.

[3074] 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.

patient had a baseline TG level > 500 mg/dL.[3075] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[3076] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[3077] Based on this disclosure, only one patient definitively had a baseline TG level ≥ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[3078] In Takaku, three patients had baseline TG levels above 500 mg/dL.[3079] However, the mean baseline TG level for all patients was 245 mg/dL.[3080] Indeed, the mean baseline TG level of the patients in all three studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[3081] Defendants have failed to identify all of the claimed elements and fail to provide motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

[3075] Nakamura at 23, Table 1.

[3076] Nakamura at 23, Tables 1 and 2.

[3077] *Id.* at 23.

[3078] *Id.* at 10.

[3079] Takaku at ICOSAPENT_DFNDTS00006895.

[3080] Takaku at ICOSAPENT_DFNDTS00006875.

[3081] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[3082] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[3083] In fact, Defendants acknowledge in their Joint Invalidity Contentions that "DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[3084] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[3085] Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

[3082] Defendants' Joint Invalidity Contentions at 447.

[3083] Mori 2006 at 98.

[3084] Defendants' Joint Invalidity Contentions at 451.

[3085] 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 grater with DHA supplementation than EPA supplementation).

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[3086] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[3087] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia, because these studies were not designed to determine the effect of dose on the degree of TG reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[3088] Therefore, a person of ordinary skill would not have been motivated to

[3086] Defendants' Joint Invalidity Contentions at 447.

[3087] Defendants' Joint Invalidity Contentions at 447.

[3088] *See* Section III.

administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl."[3089] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy."[3090] Defendants first support this argument by asserting that a person of ordinary skill in the art would have known that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA

[3089] Defendants' Joint Invalidity Contentions at 447.

[3090] Defendants' Joint Invalidity Contentions at 438.

to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition,[3091] however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[3092]

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

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[3093] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[3094]

Defendants rely on Kelley and the Lovaza label to argue that "one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in

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[3091] Defendants' Joint Invalidity Contentions at 448-49.

[3092] *See* Section IV.

[3093] Defendants' Joint Invalidity Contentions at 450.

[3094] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese 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.

LDL-C with DHA."[3095] However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[3096] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[3097] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[3098] (which is a reflection of total atherogenic lipoproteins)[3099] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

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

[3095] Defendants' Joint Invalidity Contentions at 451.

[3096] 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").

[3097] Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

[3098] *see* Section V.O.

[3099] *see* Section III.

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

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[3100] Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo."[3101] However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of reducing triglycerides in a subject having very-high triglyceride levels by administering purified EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore, Defendants fail to provide a reasonable expectation of success for the claimed invention.

Defendants further argue, that "because it was known that DHA and EPA were comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition with a reasonable expectation of success that such administration would result in reducing triglycerides while avoiding an increase in LDL."[3102] Defendants argument is without any basis.

[3100] Defendants' Joint Invalidity Contentions at 444.

[3101] Defendants' Joint Invalidity Contentions at 448.

[3102] Defendants' Joint Invalidity Contentions at 452.

To the contrary, because a person of ordinary skill in the art would have understood DHA and EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no explanation and cite to no article to support their argument that the similar effects on TG levels is a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected *both* EPA and DHA, whether administered alone or in combination, would cause an increase in LDL-C when administered to the very high TG patient population.

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering 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[3103]	-20%	+45%
Lovaza/Omacor[3104]	-6%	+45%

[3103] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3104] Chan 2002 I at 2381 (Table 3).

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 administrating 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.

(2) Dependent Claims

(a) Defendants Have Not Shown that Claim 2 of the '446 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.F.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 it would be obvious that a person receiving the claimed EPA compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) 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 2) 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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements, other than stating that a

patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would have been motivated to combine the elements to achieve the claimed invention.[3105]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[3106] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(b) Defendants Have Not Shown that Claim 3 of the '446 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.F.3. Because Defendants have not shown the obviousness of the Independent Claim

[3105] *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)).

[3106] *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.")

by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 3.

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.[3107] 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. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be

[3107] *Id.*

combined.[3108] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[3109] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each prior art reference as a whole.[3110] Each reference must be evaluated for all that it teaches. Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3111]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed methods of treatment, without providing a reason that would have prompted a person of ordinary skill to combine the elements.[3112] Such a naked assertion does not show why a person of

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[3108] *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").

[3109] *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").

[3110] *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).

[3111] *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").

[3112] *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)

ordinary skill would have been motivated to treat the recited patient population using the claimed methods of treatment.[3113]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[3114] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(c) Defendants Have Not Shown that Claims 4 and 5 of the '446 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.F.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 Claims 4 and 5.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to

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[3113] *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)).

[3114] *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.")

therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[3115] 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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[3116] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[3117] Defendants selectively cite to an unspecified isolated

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[3115] 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.

[3116] *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").

[3117] *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").

disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3118] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3119]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[3120] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[3121] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a

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[3118] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3119] *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").

[3120] *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)).

[3121] 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).

person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[3122] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[3123]

(d) Defendants Have Not Shown that Claim 6 of the '446 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.F.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 6.

Defendants offer no reference in support of their contention that this claim is obvious. Defendants contend, without providing any support, that it would be obvious to one of skill in the art to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. 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

[3122] *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).

[3123] *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.").

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 combined to teach the administration of the claimed EPA to very high TG patients.[3124] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3125] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3126]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment would have been obvious but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3127]

[3124] *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").

[3125] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3126] *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").

[3127] *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

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3128] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

Defendants rely on only one reference in their invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that "it was known that Apo-B is a component of LDL-C." Defendants cite to no passage or page of Theobald in connection with that argument and no support for their argument that Theobald makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all atherogenic lipoproteins.[3129]

Defendants then make the unsupported assertion that "one of ordinary skill in the art would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL syntheses." They are incorrect. Neither Defendants' characterization of Theobald nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render this claim obvious. Defendants' assertion that EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL

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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)).

[3128] *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.")

[3129] June 26, 2012 Bays Declaration; *see also* Section III.

synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with respect to this claim or Apo-B levels.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Crypthecodinium 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:[3130]

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

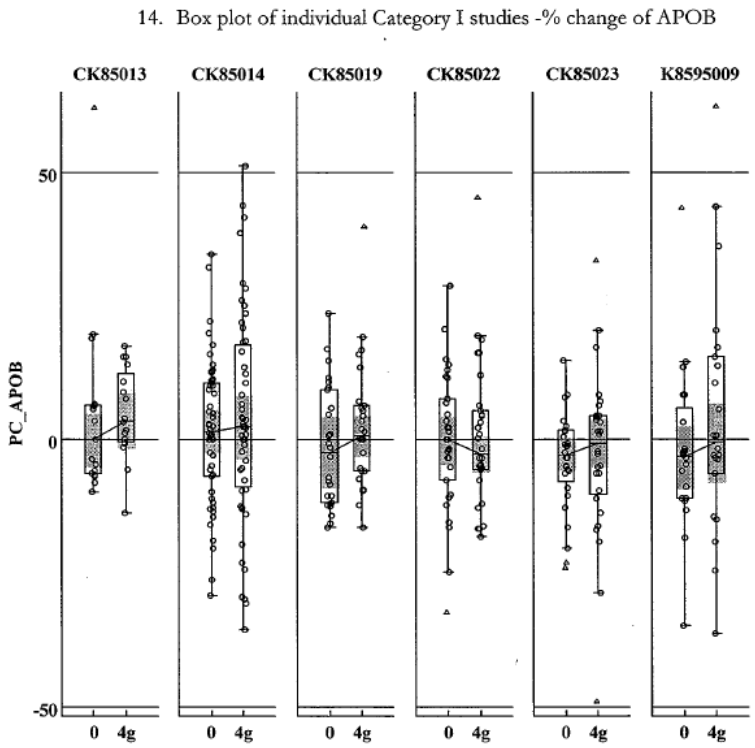
	DHA		Placebo		
	Before treatment	After treatment	Before treatment	After treatment	Treatment effect[1]
Total cholesterol (mmol/L)	5.15 ± 0.145[2]	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42)[3]
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38)[4]
HDL cholesterol (mmol/L)[5]	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)[6]	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	−0.18 (−0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)[7]
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)[3]
Weight (kg)[8]	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (−0.85, 0.24)

[1] Mean difference between active treatment and placebo; 95% CI in parentheses.
[2] $\bar{x}$ ± SEM (all such values); $n = 38$.
[3,4,7] Paired t test: [3] $P = 0.04$, [4] $P = 0.004$, [7] $P = 0.03$.
[5] HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.
[6] $n = 37$; data were log transformed before analysis by paired t test.
[8] Weight increased over the entire study period. Significant order × 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.

[3130] Theobald at 561, table 3.

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 Apo-B levels in patients with very high TG levels.[3131] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[3132]



In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[3133] there was no change in Apo-B between the control and treatment groups.

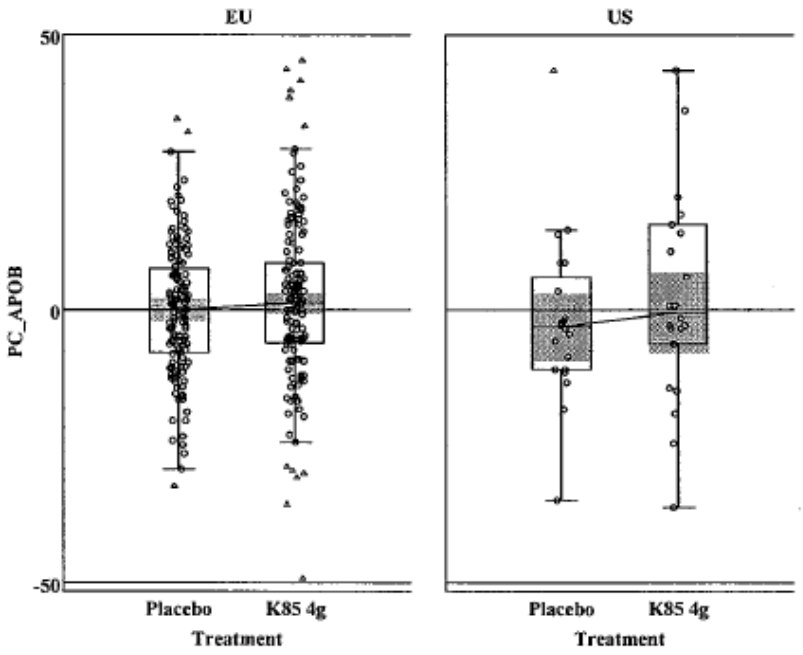
[3131] May 8, 2012 Bays Declaration.

[3132] Lovaza Approval Package at Table 14.

[3133] The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

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.[3134]

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.[3135] 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,

[3134] Lovaza Approval Package at Table 7.

[3135] *See* Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of those references, also reflecting a lack of motivation and no reasonable expectation of success.[3136]

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[3137] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[3138] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

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

[3136] Defendants' Contentions at 236.

[3137] ATP-III at 3170; Bays 2008 I at 395.

[3138] Kwiterovich in Kwiterovich at 4.

(e) Defendants Have Not Shown that Claim 7 of the '446 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.F.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 7.

Defendants contend that it would have been obvious to use the claimed composition to reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy. 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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[3139] As such, Defendants fail

[3139] *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,

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

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

(f) Defendants Have Not Shown that Claim 8, 9, 10 and 11 of the '446 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.F.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 Claims 8, 9, 10 and 11.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claims 8-11. 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

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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)).

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 combined to teach the administration of the claimed EPA to very high TG patients.[3140] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3141] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3142]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not

[3140] *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").

[3141] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3142] *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").

show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3143]

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3144] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

4. The '446 Patent is Not Invalid Under § 112

a) Defendants Have Not Demonstrated that the Claims of the '446 Patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[3145] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the art about the scope of the invention" in light of the specification and the prosecution history.[3146]

[3143] *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)).

[3144] *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.")

[3145] 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 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.

[3146] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[3147]

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[3148] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[3149] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[3150] Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

Defendants further allege that the term "a capsule . . . not more than about 3% docosahexaenoic acid or its esters, by weight of all fatty acids present" is indefinite. They

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[3147] *Id.* at 2129.

[3148] *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) ("Claim language employing terms of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the context of the invention."); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir. 2003) ("The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification.") (discussing the term "about"); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) ("It is well established that when the term 'substantially' serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite.").

[3149] *See, e.g.*, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim 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).

[3150] *See generally* the '446 patent and its prosecution history.

contend that, because there is no indication of how much of the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[3151] In light of the specification and prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[3152] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants further contend that the metes and bounds of the phrase "without substantially increasing LDL-C" are unclear. Defendants do not provide the basis for the assertion other than stating that it is unclear and the specification does not clarify its meaning. As discussed above, use of the phrase "substantially" does not render a claim *per se* indefinite. In light of the specification and the prosecution history, a person of ordinary skill in the art would know with reasonable certainty the scope of the term "without substantially increasing LDL-C" and therefore does not render the claims indefinite.[3153]

Defendants also allege that it is impossible to ascertain the metes and bounds of "a placebo control." A person of ordinary skill, however, would understand the metes and bounds of the term in light of the specification and the prosecution history.[3154] Moreover, the method of

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[3151] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. 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, 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").

[3152] *See generally* the '446 patent and its prosecution history.

[3153] *See generally* the '446 patent and its prosecution history.

[3154] *See generally* the '446 patent and its prosecution history.

comparing a subject to placebo control, such as a placebo controlled, randomized, double blind study, would have been known to a person of ordinary skill at the time of the invention. Therefore, the term does not render the claims indefinite.

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent."[3155] Plaintiffs assert that Defendants' ANDA products will be used in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '446 patent claims are not indefinite for improperly mixing methods and formulations.

b) Defendants Have Not Demonstrated that the Claims of the '446 Patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" to a skilled artisan that the applicant "invented" or "had possession" of the claimed subject matter

[3155] 35 U.S.C. § 271(c) (emphasis added).

when the application was filed.[3156] Support need not be literal[3157]—it may be implicit[3158] or inherent[3159] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[3160]

Defendants make three arguments regarding the written description requirement. First, Defendants contend that elements reciting the baseline TG levels of the asserted claims lack written description. This is incorrect. The specification of asserted patents literally discloses the claimed invention.[3161] Moreover, the recited baseline TG levels of the claimed invention appear in the original claims of the application to which the asserted patent claims priority. Thus, there is a strong presumption that the claimed invention is adequately described.[3162] Defendants do not and cannot rebut this presumption. Specifically, the patient population is originally claimed as "a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl."[3163] The asserted claims recite the same patient population. Defendants do not contend that the patient population of the asserted claims is not literally described by the specification

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[3156] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[3157] *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).

[3158] *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.

[3159] *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

[3160] *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.

[3161] *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."); *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.").

[3162] *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").

[3163] *See* U.S. Application No. 12/702,889.

and in the original claims of the application to which the asserted patent claims priority. In fact, the specification and the provisional patent application claims at the time of filing described these limitations.[3164] Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the dosages and quantities of the claimed methods.[3165] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[3166] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[3167] Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the

[3164] '446 patent at 13:29-34; 14:49-51; U.S. Application No. 12/702,889

[3165] *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."); *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.").

[3166] *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").

[3167] *See* U.S. Provisional Application No. 61/151,291.

claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants appear to suggest, although they have not specifically contended, "a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against" placebo control. Although this allegation does not appear to implicate written description, the specification describes such a comparison. Therefore, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a specific comparison of a subject or a population against a placebo control.

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[3168] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[3169]

[3168] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

[3169] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is 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

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

c) Defendants Have Not Demonstrated that the Claims of the '446 Patent Are Invalid for Lack of Enablement

The first paragraph of 35 U.S.C. § 112 requires that the specification "enable any person skilled in the art . . . to make and use [the claimed invention]." A claim is not enabled if it would require undue experimentation for a person of ordinary skill to make or use the invention. Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[3170] The enablement requirement is separate and distinct from the written description requirement,[3171] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[3172]

Defendants make two specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary

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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.").

[3170] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[3171] *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[3172] MPEP § 2164.

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

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[3173] Therefore, the claims are not invalid for lack of enablement.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '446 patent's specification enables a person of ordinary skill to obtain the claimed limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.F.3. Furthermore, Plaintiffs have initiated

[3173] *See* VASCEPA Prescribing Information at Table 2.

human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its claimed methods.[3174, 3175] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

G. The '652 Patent

1. The '652 Patent Claims Eligible Subject Matter Under § 101

Defendants' allegation that the asserted claims of the '652 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[3176] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '652 patent does not meet this requirement and thwarts the purpose of the Rules.[3177]

[3174] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical 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.").

[3175] *See* May 16, 2011 Bays Declaration at Appendix B.

[3176] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[3177] 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).

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical phenomenon, or abstract idea.[3178] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[3179]

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '652 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and] conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[3180] However, the claims merely recited this natural law without reciting any novel application of it.[3181] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[3182] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[3183]

[3178] *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) ("First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts.").

[3179] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

[3180] *Mayo*, 132 S. Ct. at 1294.

[3181] *Id.* at 1301.

[3182] *Id.*

[3183] *Id.* at 1302 (contrasting the patent-ineligible claims of that case to "a typical patent on a new drug or a new way 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).

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions make clear that EPA of the requisite purity and characteristics is not found in nature.[3184] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their natural state are patent-eligible.[3185] Moreover, Defendants' assertions are immaterial to a Section 101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[3186]

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[3187] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[3188] To say that the claims of the '652 patent claim a law of

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[3184] *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).

[3185] *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).

[3186] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

[3187] *See* Defendants' Joint Invalidity Contentions at 343.

[3188] See *CellzDirect*, 827 F.3d at 1048-49 ("The [asserted] claims are like thousands of others that recite processes 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).").

nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to underlying principles of nature" that would "make all inventions unpatentable."[3189] Indeed, even those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[3190]

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '652 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[3191] As discussed above, the asserted claims of the '652 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[3192]

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In

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[3189] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

[3190] *See Mayo*, 132 S. Ct. at 1034 ("Prometheus, supported by several *amici*, argues that a principle of law denying patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research.").

[3191] *See Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

[3192] *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 "just one step in the whole process" claimed by the invention).

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

2. The Asserted Claims of the '652 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[3193] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.[3194] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[3195] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[3196] In addition, public "possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[3197] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,

[3193] *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

[3194] *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).

[3195] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[3196] *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).

[3197] *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).

and the breadth of the claims.[3198] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[3199]

Defendants assert that Claims 1-18 of the '652 Patent are anticipated by the WO '118 reference.[3200]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference into Exhibit G, and vice-versa. WO '118 does not anticipate the claims of the '652 patent because it does not describe, properly arrange, or enable the '652 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '652 Patent

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

It is well established that, for a prior art reference to anticipate, "every element of the claimed invention must be identically shown in a single reference."[3201] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[3202] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '652 Patent: *to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline.* WO '118 further

[3198] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[3199] *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).

[3200] 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.

[3201] *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).

[3202] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

entirely fails to disclose the following elements of Claim 10 of the '652 Patent: *effective to reduce said baseline triglyceride level without substantially increasing LDL-C compared to a second patient population having said baseline triglyceride level that has not received the pharmaceutical composition.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[3203] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claims of the '652 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid

[3203] Defendants' Invalidity Contentions at 202-204.

effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[3204] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[3205] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[3206] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claims every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[3207] Rambjor is a clinical study which administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

Therefore, WO '118 cannot anticipate the independent claims of the '652 patent. Because the dependent claims include all of the claim elements of the independent claims, WO' 118 cannot anticipate any of the dependent claims as well.

[3204] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[3205] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[3206] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[3207] *See, e.g.*, Rambjor.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[3208] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[3209]

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

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[3210] The recitation of a "method of

[3208] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

[3209] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

[3210] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer 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").

reducing triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[3211] Thus, the entire preamble in the independent claims of the '652 must contain patentable weight.

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

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina."[3212] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[3213] WO '118 does not

[3211] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

[3212] WO '118 at 12.

[3213] *Id.*

expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claims.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of the reference.[3214] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

There is no evidence in that subject as described in the claims were ever treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of the subject as described in the claims. It does not. Defendants' argument rests on the definition in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL." WO '118's definition is not tied to a specific subject and there are no working examples, data or other reference in WO '118 indicating that any subject with fasting TG levels of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as evidence that a "person of ordinary skill in the art would have understood that the term 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable and then merely provides examples of commercially available "soft capsules," such as Omacor. The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be

[3214] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[3215] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claims every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '652 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[3216] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[3217] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

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[3215] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[3216] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[3217] *Atofina*, 441 F.3d at 1000.

compared to the patent's claimed range of 0.1 to 5.0 percent.[3218] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[3219] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[3220] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[3221] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),

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[3218] *Id.*

[3219] *Id.*

[3220] *See* Section III.

[3221] *Id.*

and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[3222] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[3223] Accordingly, in these populations, physicians focused on lowering LDL-C.[3224] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary treatment goal.[3225] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claims of the '652 Patent.

[3222] ATP III at 3335; *See also* Section III.

[3223] *Id.*

[3224] *Id.*

[3225] *Id.*

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

WO '118 further does not anticipate the claims of the '652 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '652 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more 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 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic

range of 330 to 450 °C,"[3226] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[3227] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[3228] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '652 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '652 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '652 patent and cannot anticipate the independent claims of the '652 Patent.

WO '118 further does not anticipate the claims of the '652 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[3229] Therefore, WO '118 discloses

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[3226] *Atofina*, 441 F.3d at 1000.

[3227] *Id.*

[3228] *Id.*

[3229] WO '118 at 22.

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

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[3230] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[3231] and therefore failed to anticipate the claimed range.[3232] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[3233] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[3234]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '652 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '652 patent. Therefore, WO '118's broad

[3230] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[3231] *Atofina*, 441 F.3d at 1000.

[3232] *Atofina*, 441 F.3d at 1000.

[3233] *Id.*

[3234] *Id.*

disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claims of the '652 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[3235] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '652 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between. There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claims of the '652 patent.

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

[3235] WO '118 at 22.

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

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

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

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

inherently anticipate as a matter of law."[3236] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[3237] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[3238] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

3. The Claims of the '652 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '652 Patent obvious.[3239] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '652 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of

[3236] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[3237] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[3238] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[3239] Defendants' Joint Invalidity Contentions at 13-25.

the '652 Patent itself to guide its combination of references.[3240] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[3241]

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

- 1) ". . .the asserted claims of the '652 patent would have been obvious over 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."

- 2) ". . .the asserted claims of the '652 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified 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."

- 3) ". . .the asserted claims of the '652 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '652 patent would have been obvious over WO '118 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."

[3240] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention 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))).

[3241] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, 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 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.

- 5) ". . . the asserted claims of the '652 patent would have been obvious over 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."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[3242] 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.[3243]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[3244] Indeed, any teaching in the art that points away from the claimed invention must be considered.[3245] A reference teaches away if a person of ordinary skill, upon reading 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.[3246] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[3247]

[3242] 35 U.S.C. § 103(a).

[3243] *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).

[3244] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011).

[3245] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999).

[3246] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[3247] *Id*.

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[3248] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[3249] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[3250]

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[3251] "[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."[3252] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[3253]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[3254] or to modify a prior art reference in a way that

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[3248] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[3249] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[3250] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

[3251] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[3252] *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))

[3253] *KSR*, 550 U.S. at 418-419.

[3254] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

"would destroy the fundamental characteristics of that reference."[3255] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[3256] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[3257] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[3258]

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[3259] and "a reasonable expectation of success."[3260]

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[3261] This protects against the use of hindsight to pick through the prior art

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[3255] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[3256] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[3257] *Id*. at 88.

[3258] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

[3259] *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).

[3260] *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).

[3261] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; 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).

based solely on structural similarity to the claimed compound.[3262] Any assertion of an "apparent reason" must find a basis in the factual record.[3263]

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[3264] including those discovered after the patent was filed or even issued.[3265] "The basic principle behind this rule is straight-forward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[3266] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[3267]

[3262] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (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).

[3263] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[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*, 619 F.3d at 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 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").

[3264] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [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.").

[3265] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

[3266] *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.").

[3267] *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

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[3268] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[3269] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[3270] These factual inquiries "guard against slipping into use of hindsight,"[3271] and "may often be the most probative and cogent evidence of nonobviousness."[3272]

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[3273]

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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.'").

[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 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.

[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 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 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.").

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

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying degrees of purity, in a wide range of doses and administration periods, to subjects who have baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[3274] Inconsistency in dosages and administration periods and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[3275] Defendants

[3274] Mori 2006 at 96.

[3275] Defendants' Joint Invalidity Contentions at 354 (*see* FN 56).

mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[3276] In addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[3277] Clinically, the authoritative guidance to physicians

[3276] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 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).

[3277] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[3278]

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

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[3279] The fibrate, Tricor (fenofibrate), for example, decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[3280]

[3278] *See* Bays Jan. 8, 2012 Decl., ¶ 22.
[3279] *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).
[3280] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[3281] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[3282] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[3283] Similar results were seen with the administration of Lopid (gemfibrozil).[3284] The differing effects of fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	**Mean Baseline TG Value**	**TG**	**LDL-C**	**HDL-C**	**Total-C**
Tricor (fenofibrate)[3285]	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.[3286] It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.[3287] 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%.[3288] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[3289]

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

[3286] Chan 2002 I at 2379-81.

[3287] *Id.; See also*, Westphal at 918.

[3288] *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

[3289] *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 [cholesteryl 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.)"

levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[3290] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[3291] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '652 patent are inherent to the compound when administered to a human subject."[3292] Inherency may not supply a missing

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[3290] Bays May 16, 2011 Decl., ¶ 11 (noting the "general knowledge in the art that omega-3 fatty acids as a class increase LDL-C" in very-high TG patients); McKenney 2007, at 724 ("Because of the increase in LDL levels 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.").

[3291] Bays 2008 I at 400-402.

[3292] Defendants' Joint Invalidity Contentions at 355.

claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[3293] Obviousness is based on what is *known* in the art at the time of the invention.[3294] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[3295] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

Defendants argue that the claims of the '652 patent which contain "a limiting clause, such as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively recited and therefore are not elements.[3296] This is incorrect. "There is nothing inherently wrong with defining some part of an invention in functional terms."[3297] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[3298] The claim term "to effect" acts as a positive limitation if the term represents

[3293] *See, e.g.*, *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) ("A party must . . . 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).

[3294] *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.").

[3295] *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

[3296] Defendants' Joint Invalidity Contentions at 356.

[3297] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

[3298] Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

"unexpected and improved effects of administration of the claimed compound."[3299] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

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

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

(1) WO '118

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '652 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited

[3299] 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).

portions of WO ‘118 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage.

With respect to Claims 1 and 10 of the ‘652 Patent (and therefore all asserted claims), WO ‘118 does not disclose or suggest a subject with the recited very high TG level. WO ‘118 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or dosage. With respect to claim 1, the cited portions of WO ‘118 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of WO ‘118 further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(2) WO ’900

WO ‘900 describes methods for obtaining EPA-rich compositions.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '900 disclose or suggest elements of the '652 Claims. The cited portions of WO '900 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. With respect to claim 1, the cited portions of WO '900 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of WO '900 further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in

Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(3) Contacos

Contacos describes a study designed to determine the safety and efficacy of a statin (pravastatin) combined with fish oil either alone or in combination, for the management of patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '652 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. With respect to claim 1, the cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the

recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(4) Grimsgaard

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of the '652 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG level.

Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or administration period. With respect to claim 1, the cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Grimsgaard further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(5) Hayashi

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

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '652 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to claim 1, the cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Hayashi further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the

claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(6) Katayama

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '652 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to claim 1, the cited portions of Katayama further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Katayama further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited

pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(7) Leigh-Firbank

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '652 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. With respect to claim 1, the

cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(8) Lovaza PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '652 Claims. The cited portions of the Lovaza PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels.

The cited portions of the Lovaza PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. With respect to claim 1, the cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(9) Maki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '652 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. With respect to claim 1, the cited portions of Maki further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of Maki further do not disclose or suggest a method of administering the claimed pharmaceutical composition that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With

respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(10) Matsuzawa

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Matsuzawa disclose or suggest elements of the '652 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Matsuzawa does not disclose or suggest a subject with the recited very high TG level. Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to claim 1, the cited portions of Matsuzawa further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Matsuzawa further do not disclose or suggest a method of administering the claimed pharmaceutical composition to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a

second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the claimed TG level.

(11) Mori 2000

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of the '652 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or administration period. With respect to claim 1, the cited portions of Mori

2000 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Mori 2000 further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(12) Mori 2006

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '652 Claims. The cited portions of Mori 2006 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited

portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. With respect to claim 1, the cited portions of Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of Mori 2006 further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '652 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '652 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also

does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to claim 1, the cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Nozaki further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(14) Omacor PDR

The Omacor PDR is the Physicians' Desk Reference describing Omacor.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '652 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Omacor PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. With respect to claim 1, the cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C. With respect to claim 10, the cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 8 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9 and 18, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '652 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or dosage. With respect to claim 1, the cited portions of Satoh further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Satoh further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to

disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(16) Shinozaki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '652 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. With respect to claim 1, the cited portions of Shinozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Shinozaki further do not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 2 and 11, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 13, this

reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '652 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage.

With respect to Claims 1 and 10 of the '652 Patent (and therefore all asserted claims), Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to claim 1, the cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG level. With respect to claim 10, the cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to reduce the recited

very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited fatty acid dosage of the recited pharmaceutical composition, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition.

Further, with respect to Claims 4 and 13, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to claims 6, 7, 15 and 16, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject or first patient population with the claimed TG level. With respect to Claims 8 and 17, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject or first patient population with the claimed TG level. With respect to Claims 9 and 18, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject or first patient population with the claimed TG level.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the ’652 Patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants’ contentions fail to disclose each and every element of the claims of the ‘652 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 10 (and therefore Claims 11-18): a pharmaceutical composition,

which when orally administered in a first patient population having said baseline triglyceride level and receiving, for a period of twelve weeks, 4 g per day of the pharmaceutical composition, is effective to reduce said baseline triglyceride level without substantially increasing LDL-C, based upon a comparison to a second patient population having said baseline triglyceride level that has not received the pharmaceutical composition. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '652 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '652 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claims of the '652 Patent Would Have Been Obvious

(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 '652 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 '652 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."[3300] Defendants also present

[3300] Defendants' Joint Invalidity Contentions at 349.

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.[3301, 3302] 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.[3303] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3304] Defendants' contentions are no

[3301] 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, Mataki, 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 Invalidity Contentions at 349.

[3302] 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 Invalidity Contentions at 347-48.

[3303] *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).

[3304] *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").

more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3305] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claims of the '652 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3306]

The analysis of the independent claims of the '652 Patent are incorporated into all asserted claims that depend from those Claims.

[3305] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3306] *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").

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '652 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.[3307] As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical

[3307] *See* Grimsgaard at 652 (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.)

guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-high or high TG patients, was expected. At the priority date of the '652 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[3308] This is an incorrect characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[3309] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor

[3308] Defendants' Joint Invalidity Contentions at 350.

[3309] Defendants' Joint Invalidity Contentions at 349-50.

would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[3310] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[3311]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In

[3310] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI_2 and PGI_3 Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[3311] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3312] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[3313] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[3314] Katayama does not disclose *any* LDL-C related data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[3315] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

[3312] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[3313] Defendants' Joint Invalidity Contentions at 350.

[3314] Katayama at 2.

[3315] *Id.* at 16.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[3316] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[3317] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[3318] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[3319] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less

[3316] Defendants' Joint Invalidity Contentions at 350.

[3317] Matsuzawa at 7 and 19.

[3318] *Id.* at 23.

[3319] *Id.* at 10.

than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[3320] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[3321] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

[3320] *Id.* at 11.

[3321] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[3322] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '652 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '652 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

[3322] *See, e.g.*, Rambjor.

Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[3323] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[3324] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[3323] Nozaki at 256.

[3324] Hayashi at 26, Table I.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3325] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[3326] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

[3325] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[3326] Defendants' Joint Invalidity Contentions at 352.

known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA

and DHA.[3327] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[3328] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[3329] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "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."[3330] Although teaching away is fact-dependent, "in general, a reference will teach

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[3327] Mori 2006 at 96.

[3328] Leigh-Firbank at 440.

[3329] *See, e.g.* Grimsgaard at 654.

[3330] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[3331]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[3332] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[3333] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[3334] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

[3331] *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.").

[3332] Mori 2000 at 1092.

[3333] Mori 2000 at 1088.

[3334] Mori 2000 at 1092.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3335] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '652 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or Hayashi, and Further in View of Grimsgaard, Mori 2000 and/or Maki

With respect to the '652 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."[3336] 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

[3335] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[3336] Defendants' Joint Invalidity Contentions at 349-50.

factual record.[3337] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3338] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3339] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375

[3337] *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).

[3338] *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").

[3339] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011).

mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '652 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3340]

The analysis of the independent claims of the '652 Patent are incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '652 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.G.3.c.1.a.i.a.i, incorporated herein by reference, Katayama

[3340] *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").

and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[3341] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[3342] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[3343] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in

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[3341] Defendants' Joint Invalidity Contentions at 353.

[3342] Defendants state in their Joint Invalidity 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).

[3343] 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."[3344] 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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[5]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[3345] 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

[3344] Defendants' Joint Invalidity Contentions at 352 n.53.

[3345] Grimsgaard at 657.

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."[3346] 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 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard 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." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[3347] A person of ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the

[3346] Grimsgaard at 654.

[3347] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to 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.

art.[3348] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[3349] based on long-term administration.[3350]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[3351] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[3352]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[3353] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in

[3348] Defendants' Joint Invalidity Contentions at 350.

[3349] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[3350] Takaku at ICOSAPENT_DFNDT00006834.

[3351] Takaku at ICOSAPENT_DFNDT00006897.

[3352] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[3353] Takaku at ICOSAPENT_DFNDT00006884.

calculating LDL-C levels when triglyceride level is above 400 mg/dL.[3354] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[3355] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other times.[3356] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[3357]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[3358] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other

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[3354] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[3355] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

[3356] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[3357] Takaku at ICOSAPENT_DFNDT00006897.

[3358] Takaku at ICOSAPENT_DFNDT00006897.

studies cited by Defendants suggest that EPA increases LDL-C.[3359] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '652 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-

[3359] *See, e.g.*, Rambjor.

B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[3360] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[3361] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes.

[3360] Nozaki at 256.

[3361] Hayashi at 26, Table I.

The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3362] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[3363] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the

[3362] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[3363] Defendants' Joint Invalidity Contentions at 352.

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

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[3364] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[3365] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with below-average levels of HDL-C levels.[3366] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,

[3364] Defendants' Joint Invalidity Contentions at 350.

[3365] Defendants' Joint Invalidity Contentions at 352.

[3366] Maki at 190.

monounsaturated and polyunsaturated fatty acids.[3367] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[3368] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have also contributed to the elevation in LDL cholesterol."[3369] Further, Maki admits that the "mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[3370] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Defendants mischaracterize the rise in LDL-C associated with the administration of omega-3 fatty acids as being a "negative effect" because they incorrectly focus on only the LDL-C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in LDL-C to be troublesome; Maki states that "the lack of increase in the total/HDL cholesterol ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level less worrisome."[3371] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the

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[3367] Maki at 191.

[3368] Maki at 195.

[3369] 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).

[3370] Maki at 197.

[3371] Maki at 197.

triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[3372]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3373] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(iii) The '652 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or in View of Satoh or Shinozaki in Further View of Contacos

With respect to the '652 Patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[3374] Defendants also present charts purporting to assert that an additional 60 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 60 separate references, they additionally do not suggest any identify 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

[3372] Maki at 197.

[3373] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[3374] Defendants' Joint Invalidity Contentions at 350.

basis in the factual record.[3375] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3376] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3377] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference would cause a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a

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[3375] *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).

[3376] *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").

[3377] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

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

Defendants formulate an obviousness argument that relies on Contacos.[3378] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[3379] or "a reasonable expectation of success"[3380] of achieving the claimed invention.

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

The proposed combinations do not render the independent claims of the '652 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO

[3378] *Id.*

[3379] *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).

[3380] *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).

considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3381]

The analysis of the independent claims of the '652 Patent are incorporated into all asserted claims that depend from those Claims.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '652 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

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

Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.G.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely confirms the safety of long term treatment of Epadel and its ability to lower both serum total 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

[3381] *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").

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

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when compared to baseline, there was no significant effect when compared to placebo.[3382] Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[3383] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C.

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

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[3382] Satoh at 145.

[3383] Defendants' Joint Invalidity Contentions at 349-50.

states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3384] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[3385] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[3386] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[3387] Defendants identify no other basis upon

[3384] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[3385] Defendants' Joint Invalidity Contentions at 349.

[3386] Shinozaki at 107-109.

[3387] *See, e.g.*, Rambjor.

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

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[3388] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement do not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels, respectively. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or Kelley —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG

[3388] Defendants' Joint Invalidity Contentions at 352.

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

Defendants rely on Geppert and/or Kelley to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[3389] Both Geppert and Kelley administer DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids. Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[3390] For example, Defendants' own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.[3391]

In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[3392] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA was the only component of fish oil to increase LDL-C. For example, there is no data comparing

[3389] Defendants' Joint Invalidity Contentions at 350.

[3390] *See* Mori 2006 at 96.

[3391] Maki at 197.

[3392] Geppert at 784.

DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying explain the mechanism of LDL-C increase.[3393] A person of ordinary skill would have not expected that EPA and DHA would have different effects on LDL-C based on Geppert.

Defendants contend that Kelley shows that DHA was responsible for the increase in LDL-C.[3394] In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[3395] Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in context with the other lipid effects reported in the study. Kelley states that:

> DHA supplementation may lower the risk of CVD by reducing plasma triacylglycerols; triaclyglycerol:HDL; the number of small, dense LDL particles; and mean diameter of VLDL particles. An increase was observed in fasting LDL cholesterol, but it is unlikely this increase is detrimental because no increase was observed in the overall number of LDL particles; actually, there was an 11% reduction that was statistically not significant. The reason LDL cholesterol increased despite no change in LDL particle number was that the LDL particles were made larger and hence more cholesterol rich by DHA treatment.[3396]

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

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[3393] *Id.*

[3394] Defendants' Joint Invalidity Contentions at 350.

[3395] Kelley at 329.

[3396] Kelley at 329

cardioprotective lipoproteins" and that "DHA supplementation may improve cardiovascular health."[3397] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with 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 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy, including administration of DHA. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

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

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3398] As is the case with Kelley, Defendants use hindsight to characterize a reference based on LDL-C levels alone without considering the other lipid effects studied, considered and reported.[3399] The isolated manner in which Defendants

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[3397] Kelley at 324, 332.

[3398] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3399] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation 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.").

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

Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3400] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert and/or Kelley.

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

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

[3400] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[3401] Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[3402] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[3403] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[3404] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

In any event, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would

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[3401] *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).

[3402] 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");

[3403] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[3404] *See Id.*, ¶ 17

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

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[3405]	-20%	+45%
Lovaza/Omacor[3406]	-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 the lack of motivation.

Defendants offer no "apparent reason" to administer EPA as claimed to patients with fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on Lovaza/Omacor as the starting point to "find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels."[3407] Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500

[3405] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3406] Chan 2002 I at 2381 (Table 3).

[3407] Defendants' Joint Invalidity Contentions at 351-52.

mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG reduction and the increased conversion of VLDL to LDL particles.[3408]

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[3409] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[3410] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels the most in patients with the highest pretreatment TG levels.[3411] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-

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[3408] *See* Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that "[t]hese 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

[3409] 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")

[3410] 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)

[3411] *See* Bays 2008 Rx Omega-3 p. 402.

C was often offset by concurrent treatment with statins.[3412] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[3413]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[3414] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[3415]

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[3416] Correspondingly, prescription omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[3417] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net

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[3412] *See* Harris 2008 at 14, McKenney at 722.

[3413] McKenney at 722-23.

[3414] *See* Westphal at 918, Harris 1997 at 389.

[3415] *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 chancing 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 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)").

[3416] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

[3417] McKenney 2007 at 722 (*see* Fig. 1).

effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the number of small, dense LDL particles to larger LDL particles.[3418] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[3419] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[3420]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[3421] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

[3418] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[3419] Stalenhoef at 134.

[3420] Harris 1997 at 389.

[3421] Defendants' Joint Invalidity Contentions at 351-52.

reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[3422] (which is a reflection of total atherogenic lipoproteins) [3423] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention.[3424] Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population,[3425] they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill

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[3422] *see* Section V.O.

[3423] *see* Section III.

[3424] *See, e.g.*, Defendants' Joint Invalidity Contentions at 347.

[3425] Defendants' Joint Invalidity Contentions at 354.

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

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

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

Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by combining the references cited by defendants. For a particular combination of references, there must be a reasonable expectation that the combination will produce the claimed invention. In this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG levels.[3426] A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG patient population. As discussed in Section III and above, it was well known that TG-lowering

[3426] As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to have the same TG lowering mechanism and would have further understood that the increase in LDL-C 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[3427]	-20%	+45%
Lovaza/Omacor[3428]	-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.[3429]

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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.[3430] 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,

[3427] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3428] Chan 2002 I at 2381 (Table 3).

[3429] 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.

[3430] 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.

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. 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.

Defendants argue that because Grimsgaard administered purified ethyl EPA to patients with borderline-high/high TG, it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.[3431] Defendants' contentions are no more than a demonstration that certain claim elements was known in the prior art and demonstrates impermissible hindsight reconstruction.[3432] As is reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,

[3431] Defendants' Joint Invalidity Contentions at 354.

[3432] *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.").

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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[3]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

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 Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[3433] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[3434] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

Defendants argue that a person of ordinary skill at the time of the invention, based on studies in normal, borderline-high and high TG patients, knew that administration of DHA alone resulted in undesirable increased LDL-C levels while administration of EPA alone had little to no impact on LDL-C levels.[3435] However, that statement does not conform with what was known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor

[3433] *See Sanofi*, 748 F.3d at 1360–61.

[3434] *See supra* Section III.

[3435] Defendants' Joint Invalidity Contentions at 353.

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

With the lack of any reasonable expectation of success, Defendants argue that their proposed combination amounts to a simple substitution of one known element for another, and that that these changes yield predictable results.[3436] Such an argument, however, represents pure and impermissible hindsight bias and further does not consider that reasons for which a person of ordinary skill would not be motivated to combine these references and affirmatives ways in which the art taught away from these combinations.

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

(i) The '652 Patent is not Obvious Over WO '118 or WO '900, in Combination with the Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '652 Patent, Defendants present a combination of five references: "WO '118 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."[3437] Defendants also present charts arguing 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

[3436] Defendants' Joint Invalidity Contentions at 3355.

[3437] Defendants' Joint Invalidity Contentions at 356-57.

combining these references.[3438, 3439] 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.[3440] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3441] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

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[3438] Defendants' bare assertion that the asserted claims are obvious "in view of one or more of the references cited in Sections III and V.A. and B., including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, 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 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.

[3439] 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 Invalidity Contentions at 347.

[3440] *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) (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 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).

[3441] *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").

that it teaches.[3442] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[3443] Contrary to Defendants' assertion that WO '118 discloses "the administration of 4 g of pure EPA with no DHA,"[3444] WO '118 fails to disclose the claimed subject with the specified very high TG levels (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[3445]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[3446] WO '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to

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[3442] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3443] WO '118 at 9.

[3444] Defendants' Joint Invalidity Contentions at 357.

[3445] WO '118 at 22-23.

[3446] WO '118 at 8.

patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[3447]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[3448] WO '118 states that "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[3449] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[3450] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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

[3447] *See* Section III.

[3448] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

[3449] WO '118 at 22-23.

[3450] WO '118 at 23.

WO ‘900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[3451] Moreover, WO ‘900 does not teach the desired effect of EPA other than commenting generally that it “may promote health and ameliorate or even reverse the effects of a range of common diseases.”[3452] It has no discussion, for example, on any TG-lowering effect of EPA. Although WO ‘900 identifies DHA as an “undesired molecule”, it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than commenting generally that “the desired effects of EPA may be limited or reversed” by them.[3453] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claims of the ’652 Patent obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO considered WO ‘118, WO ‘900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3454]

The analysis of the independent claims of the ‘652 patent are incorporated into all asserted claims that depend from those Claims.

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge

[3451] *See, e.g.*, ’900 Pub. at 16-17.

[3452] ’900 Pub. at 5.

[3453] ’900 Pub. at 39.

[3454] *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”).

that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[3455]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. 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.[3456] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3457] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

[3455] Defendants' Joint Invalidity Contentions at 357.

[3456] *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).

[3457] *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").

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

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3458] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '652 Patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in

[3458] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

View of Katayama, Matsuzawa and/or Takaku.

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."[3459] 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.[3460] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3461] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

[3459] Defendants' Joint Invalidity Contentions at 357.

[3460] *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).

[3461] *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").

Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3462] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[3463] 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

[3462] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3463] Defendants' Joint Invalidity Contentions at 357.

record.[3464] Defendants' assertions related to motivation are insufficient,[3465] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[3466] or "a reasonable expectation of success"[3467] of achieving the claimed invention. Therefore, Defendants should be precluded from relying on this these references.

As discussed above in Section V.G.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only designed to confirm the safety of long term treatment of Epadel and its ability to lower both

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[3464] *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).

[3465] 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 358.

[3466] *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).

[3467] *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).

serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population and do not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. As discussed above in Section V.G.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[3468] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[3469]

The proposed combination does not render the independent claims of the '652 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3470]

The analysis of the independent claims of the '652 patent are incorporated into all asserted claims that depend from those Claims.

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

[3468] Takaku at ICOSAPENT_DFNDT00006897.

[3469] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[3470] *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").

Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[3471]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.G.3.c.1.a.ii.a.iii is incorporated herein by reference. A person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[3472] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is

[3471] Defendants' Joint Invalidity Contentions at 358.

[3472] 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.

administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[3473] However, one of ordinary skill in the art knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[3474] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3475] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[3476] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

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[3473] Maki at 195.

[3474] 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.").

[3475] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[3476] Defendants' Joint Invalidity Contentions at 358.

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

Indeed, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[3477]	-20%	+45%
Lovaza/Omacor[3478]	-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

[3477] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3478] Chan 2002 I at 2381 (Table 3).

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."[3479] 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.[3480] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not."[3481] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[3482] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with other saturated and polyunsaturated fatty acids.[3483] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[3484] Kelley does not show that

[3479] Defendants' Joint Invalidity Contentions at 358-59.

[3480] 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.

[3481] Defendants' Joint Invalidity Contentions at 363.

[3482] The discussion related to Leigh-Firbank in Section V.G.3.c.1.a.i.a.iii is incorporated herein by reference.

[3483] The discussion related to Kelley in Section V.G.3.c.1.a.iii.a.ii is incorporated herein by reference.

[3484] *See* Mori 2006 at 96.

DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[3485] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[3486] Finally, Theobald also does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid. Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[3487]Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[3488] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after

[3485] Kelley at 329.

[3486] 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.")

[3487] *See* Mori 2006 at 96.

[3488] Defendants' Joint Invalidity Contentions at 358.

EPA supplementation."[3489] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA," the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been well documented.[3490] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[3491] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[3492] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[3493]

[3489] Mori 2000 at 1092.

[3490] 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.

[3491] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[3492] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[3493] Harris 2008 at 13.

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."[3494] As discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[3495]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that DHA is *more* cardioprotective than EPA.[3496] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[3497] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[3498] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[3499] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA

[3494] Defendants' Joint Invalidity Contentions at 339.

[3495] 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").

[3496] Harris 2007 at 8.

[3497] *Id.*

[3498] 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.").

[3499] *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 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.").

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

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[3500] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[3501]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[3502] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[3503] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG

[3500] Defendants' Joint Invalidity Contentions at 360-61.

[3501] Defendants' Joint Invalidity Contentions at 361.

[3502] *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.").

[3503] Nakamura, Matsuzawa, and Takaku.

levels > 500 mg/dL."[3504],[3505] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one patient had a baseline TG level > 500 mg/dL.[3506] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[3507] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[3508] Based on this disclosure, only one patient definitively had a baseline TG level $\geq$ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[3509] In Takaku, three patients had baseline TG levels above 500 mg/dL.[3510] However, the mean baseline TG level for all patients was 245 mg/dL.[3511] Indeed, the mean baseline TG level of the patients in all three studies was well below

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[3504] Defendants' Joint Invalidity Contentions at 360.

[3505] 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.

[3506] Nakamura at 23, Table 1.

[3507] Nakamura at 23, Tables 1 and 2.

[3508] *Id.* at 23.

[3509] *Id.* at 10.

[3510] Takaku at ICOSAPENT_DFNDTS00006895.

[3511] Takaku at ICOSAPENT_DFNDTS00006875.

500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[3512] Defendants have failed to identify all of the claimed elements and fail to provide motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[3513] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[3514] In fact, Defendants acknowledge in their Joint Invalidity Contentions that

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[3512] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

[3513] Defendants' Joint Invalidity Contentions at 361.

[3514] Mori 2006 at 98.

"DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[3515] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[3516] Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[3517] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[3518] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,

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[3515] Defendants' Joint Invalidity Contentions at 365.

[3516] 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 grater with DHA supplementation than EPA supplementation).

[3517] Defendants' Joint Invalidity Contentions at 361.

[3518] Defendants' Joint Invalidity Contentions at 361.

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

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[3519] Therefore, a person of ordinary skill would not have been motivated to administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl."[3520] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

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

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[3519] *See* Section III.

[3520] Defendants' Joint Invalidity Contentions at 361-62.

reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy."[3521] Defendants first support this argument by asserting that a person of ordinary skill in the art would have known that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition,[3522] however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[3523]

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

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[3524] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that

[3521] Defendants' Joint Invalidity Contentions at 363.

[3522] Defendants' Joint Invalidity Contentions at 363.

[3523] *See* Section IV.

[3524] Defendants' Joint Invalidity Contentions at 365.

the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[3525]

Defendants rely on Kelley and the Lovaza label to argue that "one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in LDL-C with DHA."[3526] However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[3527] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[3528] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

[3525] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese 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.

[3526] Defendants' Joint Invalidity Contentions at 365.

[3527] 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").

[3528] Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[3529] (which is a reflection of total atherogenic lipoproteins)[3530] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

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

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

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[3531] Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo."[3532] However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of

[3529] *see* Section V.O.

[3530] *see* Section III.

[3531] Defendants' Joint Invalidity Contentions at 358.

[3532] Defendants' Joint Invalidity Contentions at 362.

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

Defendants further argue, that "because it was known that DHA and EPA were comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition with a reasonable expectation of success that such administration would result in reducing triglycerides while avoiding an increase in LDL."[3533] Defendants argument is without any basis. To the contrary, because a person of ordinary skill in the art would have understood DHA and EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no explanation and cite to no article to support their argument that the similar effects on TG levels is a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected *both* EPA and DHA, whether administered alone or in combination, would cause an increase in LDL-C when administered to the very high TG patient population.

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering agents, specifically fibrates and

[3533] Defendants' Joint Invalidity Contentions at 366.

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[3534]	-20%	+45%
Lovaza/Omacor[3535]	-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 using EPA.

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating 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 '652 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

[3534] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3535] Chan 2002 I at 2381 (Table 3).

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.

(2) Dependent Claims

(a) Defendants Have Not Shown that Claims 2 and 11 of the '652 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 2 and 11.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claims 2 and 11. 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 combined to teach the administration of the claimed EPA to very high TG patients.[3536] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3537] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3538]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3539]

[3536] *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").

[3537] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3538] *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").

[3539] *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

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3540] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(b) Defendants Have Not Shown that Claims 3 and 12 of the '652 Patent Would Have Been Obvious

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

Defendants contend, without providing meaningful support, that the claim element was well known in the art. 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'

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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)).

[3540] *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.")

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. Defendants make a conclusory statement that the claimed method of treatment was well known in the art, but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3541] Further Defendants cite to the "Lovaza product" without identifying the prior art reference to which they refer. Such a reference is inadequate.

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3542] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(c) Defendants Have Not Shown that Claims 4 and 13 of the '652 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 4 and 13.

[3541] *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)).

[3542] *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.")

Defendants contend that it would be obvious that a person receiving the claimed EPA compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) 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 2) 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. Defendants merely demonstrate that the element was purported known in the prior art without explaining how it can be combined with other elements.[3543] As such, Defendants discuss the claim element in isolation, and fail to address the claimed invention as a whole.[3544] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference,

[3543] *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").

[3544] *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").

however, must be evaluated for all that it teaches.[3545] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3546]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements, other than stating that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would have been motivated to combine the elements to achieve the claimed invention.[3547]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that

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[3545] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3546] *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").

[3547] *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)).

purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[3548] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(d) Defendants Have Not Shown that Claims 5 and 14 of the '652 Patent Would Have Been Obvious

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

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.[3549] 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

[3548] *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.")

[3549] *Id.*

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. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be combined.[3550] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[3551] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each prior art reference as a whole.[3552] Each reference must be evaluated for all that it teaches. Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3553]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a

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[3550] *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").

[3551] *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").

[3552] *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).

[3553] *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").

conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed methods of treatment, without providing a reason that would have prompted a person of ordinary skill to combine the elements.[3554] Such a naked assertion does not show why a person of ordinary skill would have been motivated to treat the recited patient population using the claimed methods of treatment.[3555]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[3556] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

[3554] *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)

[3555] *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)).

[3556] *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.")

(e) Defendants Have Not Shown that Claims 6, 7, 15 and 16 of the '652 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 6, 7, 15 and 16.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[3557] 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,

[3557] 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.

Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants further contend, without support, that a person of ordinary skill would "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude, without support, that it would have been obvious to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing triglycerides while avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) 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 3) 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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[3558] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[3559] Defendants selectively cite to an unspecified isolated

[3558] *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").

[3559] *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").

disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3560] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3561]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[3562] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[3563] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a

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[3560] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3561] *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").

[3562] *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)).

[3563] 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).

person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[3564] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[3565]

(f) Defendants Have Not Shown that Claims 8 and 17 of the '652 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 8 and 17.

Defendants offer no reference in support of their contention that these claims are obvious. Defendants contend, without providing any support, that it would be obvious to one of skill in the art to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. 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

[3564] *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).

[3565] *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.").

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 combined to teach the administration of the claimed EPA to very high TG patients.[3566] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3567] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3568]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment would have been obvious but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3569]

[3566] *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").

[3567] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3568] *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").

[3569] *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

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3570] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

Defendants rely on only one reference in their invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that "it was known that Apo-B is a component of LDL-C." Defendants cite to no passage or page of Theobald in connection with that argument and no support for their argument that Theobald makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all atherogenic lipoproteins.[3571]

Defendants then make the unsupported assertion that "one of ordinary skill in the art would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL syntheses." They are incorrect. Neither Defendants' characterization of Theobald nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render this claim obvious. Defendants' assertion that EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL

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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)).

[3570] *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.")

[3571] June 26, 2012 Bays Declaration; *see also* Section III.

synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with respect to these claims or Apo-B levels.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Crypthecodinium 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:[3572]

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

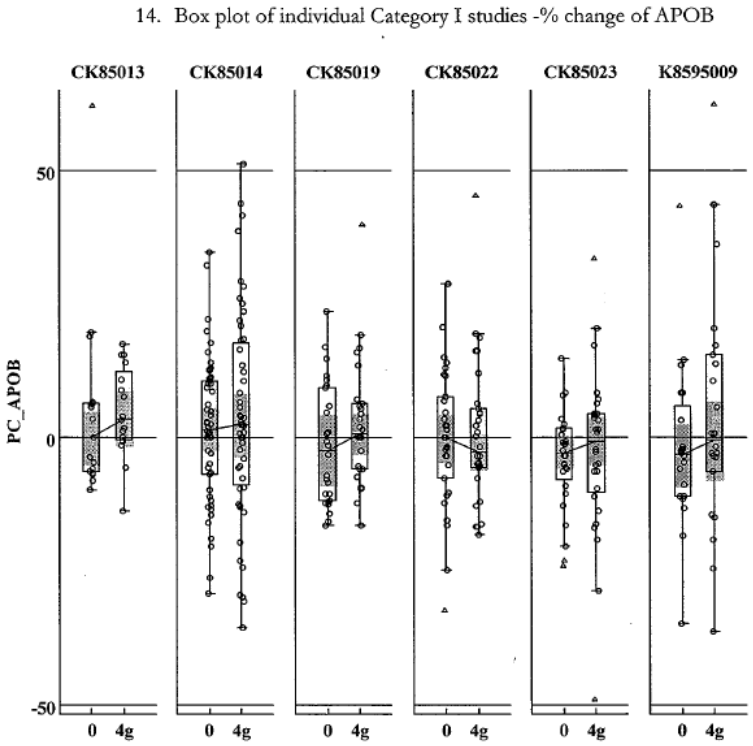
	DHA		Placebo		
	Before treatment	After treatment	Before treatment	After treatment	Treatment effect[1]
Total cholesterol (mmol/L)	5.15 ± 0.145[2]	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42)[3]
LDL cholesterol (mmol/L)	3.16 ± 0.129	3.48 ± 0.152	3.16 ± 0.146	3.25 ± 0.131	0.23 (0.08, 0.38)[4]
HDL cholesterol (mmol/L)[5]	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)[6]	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	−0.18 (−0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)[7]
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)[3]
Weight (kg)[8]	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (−0.85, 0.24)

[1] Mean difference between active treatment and placebo; 95% CI in parentheses.
[2] $\bar{x}$ ± SEM (all such values); $n = 38$.
[3,4,7] Paired t test: [3] $P = 0.04$, [4] $P = 0.004$, [7] $P = 0.03$.
[5] HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.
[6] $n = 37$; data were log transformed before analysis by paired t test.
[8] Weight increased over the entire study period. Significant order × 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.

[3572] Theobald at 561, table 3.

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 Apo-B levels in patients with very high TG levels.[3573] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[3574]



In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[3575] there was no change in Apo-B between the control and treatment groups.

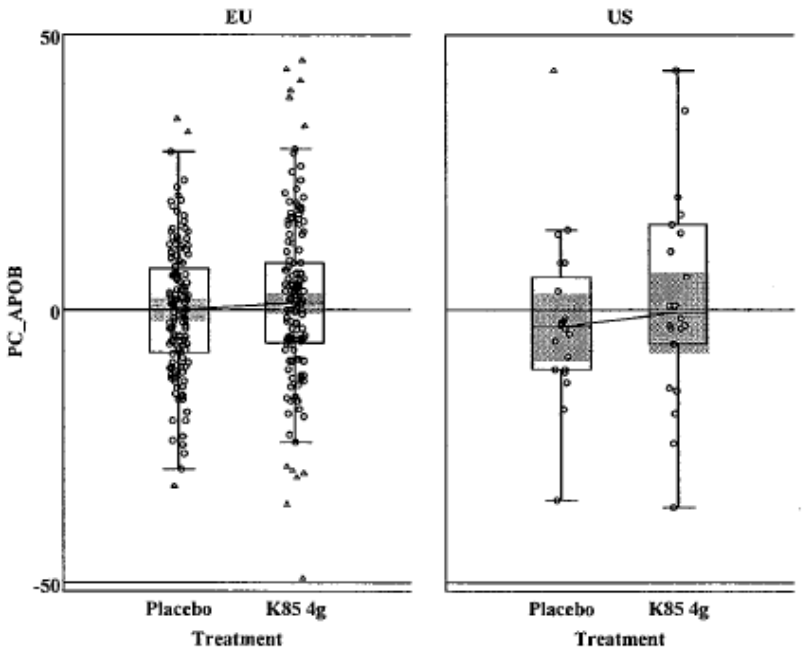
[3573] May 8, 2012 Bays Declaration.

[3574] Lovaza Approval Package at Table 14.

[3575] The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

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.[3576]

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.[3577] 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,

[3576] Lovaza Approval Package at Table 7.

[3577] *See* Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of those references, also reflecting a lack of motivation and no reasonable expectation of success.[3578]

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[3579] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[3580] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

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

[3578] Defendants' Contentions at 236.

[3579] ATP-III at 3170; Bays 2008 I at 395.

[3580] Kwiterovich in Kwiterovich at 4.

(g) Defendants Have Not Shown that Claims 9 and 18 of the '652 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.G.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 9 and 18.

Defendants contend that it would have been obvious to use the claimed composition to reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy. 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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[3581] As such, Defendants fail

[3581] *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,

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

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

4. The '652 Patent is Not Invalid Under § 112

a) Defendants Have Not Demonstrated that the Claims of the '652 patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[3582] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the art about the scope of the invention" in light of the specification and the prosecution history.[3583]

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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)).

[3582] 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 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.

[3583] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[3584]

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[3585] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[3586] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[3587] Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

Defendants further allege that the term "4g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate" is

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[3584] *Id.* at 2129.

[3585] *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) ("Claim language employing terms of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the context of the invention."); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir. 2003) ("The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification.") (discussing the term "about"); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) ("It is well established that when the term 'substantially' serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite.").

[3586] *See, e.g.*, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim 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).

[3587] *See generally* the '652 patent and its prosecution history.

indefinite. They contend that, because there is no indication of how much of the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[3588] In light of the specification and prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[3589] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants further allege that the term "compared to baseline" is indefinite. Defendants, again, provide no basis for this allegation. In light of the specification and the prosecution history, a person of ordinary skill would know with reasonable certainty the scope of the term "compared to baseline" and therefore does not render the claims indefinite.

Defendants also allege that it is impossible to ascertain the metes and bounds of "a first patient population having said baseline triglyceride level" and "a second patient population having said baseline triglycerides level." A person of ordinary skill, however, would understand the metes and bounds of the terms in light of the specification and the prosecution history.[3590] Moreover, the method of comparing a subject to a second subject, such as a placebo controlled, randomized, double blind study, would have been known to a person of ordinary skill at the time of the invention. Therefore, the term does not render the claims indefinite.

[3588] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. 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, 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").

[3589] *See generally* the '652 patent and its prosecution history.

[3590] *See generally* the '652 patent and its prosecution history.

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent."[3591] Plaintiffs assert that Defendants' ANDA products will be used in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '652 patent claims are not indefinite for improperly mixing methods and formulations.

b) Defendants Have Not Demonstrated that the Claims of the '652 patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" to a skilled artisan that the applicant "invented" or "had possession" of the claimed subject matter when the application was filed.[3592] Support need not be literal[3593]—it may be implicit[3594] or

[3591] 35 U.S.C. § 271(c) (emphasis added).

[3592] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[3593] *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).

[3594] *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.

inherent[3595] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[3596]

Defendants make three arguments regarding the written description requirement. First, Defendants contend that elements reciting the baseline TG levels of the asserted claims lack written description. This is incorrect. The specification of asserted patents literally discloses the claimed invention.[3597] Moreover, the recited baseline TG levels of the claimed invention appear in the original claims of the application to which the asserted patent claims priority. Thus, there is a strong presumption that the claimed invention is adequately described.[3598] Defendants do not and cannot rebut this presumption. Specifically, the patient population is originally claimed as "a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl."[3599] The asserted claims recite the same patient population. Defendants do not contend that the patient population of the asserted claims is not literally described by the specification and in the original claims of the application to which the asserted patent claims priority. In fact, the specification and the provisional patent application claims at the time of filing describe these limitations.[3600] Therefore, Defendants have failed to explain whether and how an aspect of the

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[3595] *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

[3596] *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.

[3597] *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."); *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.").

[3598] *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").

[3599] *See* U.S. Application No. 12/702,889.

[3600] '652 patent at 13:29-34; 14:49-51; U.S. Provisional Application No. 61/151,291.

claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the dosages and quantities of the claimed methods.[3601] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[3602] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[3603] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against a second subject or

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[3601] *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."); *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.").

[3602] *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").

[3603] *See* U.S. Provisional Application No. 61/151,291.

against a second population." The specification demonstrates that the applicants were in possession of the claimed inventions. For example, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a specific comparison of a subject or a population against a second subject, baseline, or a second population.

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[3604] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[3605] Written description requires only that the specification reasonably conveys that the applicant had possession of the claimed subject matter when the application was filed. Therefore, whether the claims are obvious has no bearing on the adequacy of written description.

[3604] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

[3605] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is 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 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.").

c) Defendants Have Not Demonstrated that the Claims of the '652 patent Are Invalid for Lack of Enablement

The first paragraph of 35 U.S.C. § 112 requires that the specification "enable any person skilled in the art . . . to make and use [the claimed invention]." A claim is not enabled if it would require undue experimentation for a person of ordinary skill to make or use the invention. Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[3606] The enablement requirement is separate and distinct from the written description requirement,[3607] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[3608]

Defendants make two specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary skill would be able to determine the amounts of the components in the pharmaceutical composition without any experimentation, much less undue experimentation.

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited

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[3606] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[3607] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[3608] MPEP § 2164.

composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[3609] Therefore, the claims are not invalid for lack of enablement.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '652 patent's specification enables a person of ordinary skill to obtain the claimed limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.G.3. Furthermore, Plaintiffs have initiated human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its claimed methods.[3610, 3611] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

[3609] *See* VASCEPA Prescribing Information at Table 2.

[3610] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical 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.").

[3611] *See* May 16, 2011 Bays Declaration at Appendix B.

H. **The '920 Patent**

1. The '920 Patent Claims Eligible Subject Matter Under § 101

Defendants' allegation that the asserted claims of the '920 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[3612] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '920 patent does not meet this requirement and thwarts the purpose of the Rules.[3613]

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical phenomenon, or abstract idea.[3614] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[3615]

[3612] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[3613] Nor does the preceding paragraph, which provides only a purported summary of the claims of the '920 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).

[3614] *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) ("First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts.").

[3615] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '920 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and] conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[3616] However, the claims merely recited this natural law without reciting any novel application of it.[3617] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[3618] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[3619]

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions make clear that EPA of the requisite purity and characteristics is not found in nature.[3620] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their

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[3616] *Mayo*, 132 S. Ct. at 1294.

[3617] *Id.* at 1301.

[3618] *Id.*

[3619] *Id.* at 1302 (contrasting the patent-ineligible claims of that case to "a typical patent on a new drug or a new way 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).

[3620] *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).

natural state are patent-eligible.[3621] Moreover, Defendants' assertions are immaterial to a Section 101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[3622]

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[3623] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[3624] To say that the claims of the '920 patent claim a law of nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to underlying principles of nature" that would "make all inventions unpatentable."[3625] Indeed, even

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[3621] *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).

[3622] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

[3623] *See* Defendants' Joint Invalidity Contentions at 388.

[3624] See *CellzDirect*, 827 F.3d at 1048-49 ("The [asserted] claims are like thousands of others that recite processes 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).").

[3625] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[3626]

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '920 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[3627] As discussed above, the asserted claims of the '920 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[3628]

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In addition, as discussed above, the asserted claims are not merely a naturally-occurring phenomena, and thus satisfy the requirements of § 101.

[3626] *See Mayo*, 132 S. Ct. at 1034 ("Prometheus, supported by several *amici*, argues that a principle of law denying patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research.").

[3627] *See Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

[3628] *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 "just one step in the whole process" claimed by the invention).

2. The Asserted Claims of the '920 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[3629] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.[3630] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[3631] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[3632] In addition, public "possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[3633] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[3634] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[3635]

[3629] *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

[3630] *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).

[3631] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[3632] *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).

[3633] *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).

[3634] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[3635] *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).

Defendants assert that Claims 1-10 of the '920 Patent are anticipated by the WO '118 reference.[3636]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference into Exhibit H, and vice-versa. WO '118 does not anticipate the claims of the '920 patent because it does not describe, properly arrange, or enable the '920 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '920 Patent

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

It is well established that, for a prior art reference to anticipate, "every element of the claimed invention must be identically shown in a single reference."[3637] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[3638] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '920 Patent: *to effect a reduction in triglycerides compared to baseline.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[3639] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that

[3636] 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.

[3637] *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).

[3638] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

[3639] Defendants' Invalidity Contentions at 202-204.

is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claim of the '920 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[3640] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[3641] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[3642] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets

[3640] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[3641] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[3642] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

the elements of the independent claim every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[3643] Rambjor is a clinical study which administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

Therefore, WO '118 cannot anticipate the independent claim of the '920 patent. Because the dependent claims include all of the claim elements of the independent claim, WO' 118 cannot anticipate any of the dependent claims as well.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning,

[3643] *See, e.g.*, Rambjor.

and vitality' to the claim."[3644] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[3645]

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

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[3646] The recitation of a "method of reducing triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[3647] Thus, the entire preamble in the independent claim of the '920 must contain patentable weight.

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

[3644] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

[3645] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

[3646] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer 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").

[3647] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina."[3648] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[3649] WO '118 does not expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claim.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of the reference.[3650] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

There is no evidence in that subject as described in the claims were ever treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of

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[3648] WO '118 at 12.

[3649] *Id.*

[3650] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

the subject as described in the claims. It does not. Defendants' argument rests on the definition in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL." WO '118's definition is not tied to a specific subject and there are no working examples, data or other reference in WO '118 indicating that any subject with fasting TG levels of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as evidence that a "person of ordinary skill in the art would have understood that the term 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable and then merely provides examples of commercially available "soft capsules," such as Omacor. The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[3651] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claim every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '920 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and

[3651] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[3652] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[3653] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as compared to the patent's claimed range of 0.1 to 5.0 percent.[3654] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[3655] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of

[3652] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[3653] *Atofina*, 441 F.3d at 1000.

[3654] *Id.*

[3655] *Id.*

cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[3656] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[3657] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL), and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[3658] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[3659] Accordingly, in these populations, physicians focused on lowering LDL-C.[3660] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary

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[3656] *See* Section III.

[3657] *Id.*

[3658] ATP III at 3335; *See also* Section III.

[3659] *Id.*

[3660] *Id.*

treatment goal.[3661] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claim of the '920 Patent.

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

WO '118 further does not anticipate the claims of the '920 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '920 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more

[3661] *Id.*

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 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[3662] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[3663] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[3664] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '920 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range

[3662] *Atofina*, 441 F.3d at 1000.

[3663] *Id.*

[3664] *Id.*

claimed by the '920 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '920 patent and cannot anticipate the independent claim of the '920 Patent.

WO '118 further does not anticipate the claims of the '920 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[3665] Therefore, WO '118 discloses EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed generic range for the EPA composition in the claimed pharmaceutical composition.

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[3666] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[3667] and therefore failed

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[3665] WO '118 at 22.

[3666] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[3667] *Atofina*, 441 F.3d at 1000.

to anticipate the claimed range.[3668] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[3669] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[3670]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '920 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '920 patent. Therefore, WO '118's broad disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claim of the '920 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[3671] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '920 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.

[3668] *Atofina*, 441 F.3d at 1000.

[3669] *Id.*

[3670] *Id.*

[3671] WO '118 at 22.

There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claim of the '920 patent.

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

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

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

Defendants fail to address any of the claim elements of the dependent claims. Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail

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

Further, Defendants entirely fail to prove that inherently discloses the recited claim limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[3672] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[3673] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[3674] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in

[3672] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[3673] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[3674] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

3. The Claims of the '920 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '920 patent obvious.[3675] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '920 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of the '920 patent itself to guide its combination of references.[3676] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[3677]

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

[3675] Defendants' Joint Invalidity Contentions at 13-25.

[3676] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention 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))).

[3677] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, 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 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) ". . .the asserted claims of the '920 patent would have been obvious over 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."

- 2) ". . .the asserted claims of the '920 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified 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."

- 3) ". . .the asserted claims of the '920 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '920 patent would have been obvious over WO '118 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."

- 5) ". . . the asserted claims of the '920 patent would have been obvious over 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."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[3678] 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.[3679]

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

[3678] 35 U.S.C. § 103(a).

[3679] *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).

teaches, including the portions that would lead away from the claimed invention.[3680] Indeed, any teaching in the art that points away from the claimed invention must be considered.[3681] A reference teaches away if a person of ordinary skill, upon reading 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.[3682] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[3683]

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[3684] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[3685] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[3686]

"The determination of obviousness is made with respect to the subject matter as a whole,

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[3680] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3681] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

[3682] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[3683] *Id.*

[3684] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[3685] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[3686] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

not separate pieces of the claim."[3687] "[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."[3688] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[3689]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[3690] or to modify a prior art reference in a way that "would destroy the fundamental characteristics of that reference."[3691] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[3692] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[3693] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[3694]

[3687] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[3688] *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))

[3689] *KSR*, 550 U.S. at 418-419.

[3690] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

[3691] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[3692] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[3693] *Id*. at 88.

[3694] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[3695] and "a reasonable expectation of success."[3696]

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[3697] This protects against the use of hindsight to pick through the prior art based solely on structural similarity to the claimed compound.[3698] Any assertion of an "apparent reason" must find a basis in the factual record.[3699]

[3695] *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).

[3696] *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).

[3697] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; 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).

[3698] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (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).

[3699] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[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*, 619 F.3d at 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 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").

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[3700] including those discovered after the patent was filed or even issued.[3701] "The basic principle behind this rule is straight-forward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[3702] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[3703]

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[3704] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[3705] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or

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[3700] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [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.").

[3701] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

[3702] *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.").

[3703] *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.'").

[3704] *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).

[3705] *Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1569 (Fed. Cir. 1987).

surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[3706] These factual inquiries "guard against slipping into use of hindsight,"[3707] and "may often be the most probative and cogent evidence of nonobviousness."[3708]

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[3709]

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

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying degrees of purity, in a wide range of doses and administration periods, to subjects who have

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[3706] *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.

[3707] *Graham*, 383 U.S. at 36.

[3708] *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)).

[3709] *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.").

baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[3710] Inconsistency in dosages and administration periods and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[3711] Defendants mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[3712] In

[3710] Mori 2006 at 96.

[3711] Defendants' Joint Invalidity Contentions at 399 (*see* FN 66).

[3712] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 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).

addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[3713] Clinically, the authoritative guidance to physicians on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by

[3713] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[3714]

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

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[3715] The fibrate, Tricor (fenofibrate), for example, decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[3716] and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[3717] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[3718] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[3719] Similar results were seen with the administration of Lopid (gemfibrozil).[3720] The differing effects of

[3714] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

[3715] *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).

[3716] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3717] *Id.*

[3718] *Id. See also*, Trilipix Label at 27.

[3719] *Id. See also*, Trilipix Label at 27.

[3720] *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).

fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	**Mean Baseline TG Value**	**TG**	**LDL-C**	**HDL-C**	**Total-C**
Tricor (fenofibrate)[3721]	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

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.[3722] It had no significant effect on other lipid-related variable, including LDL-C and Apo-

[3721] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3722] Chan 2002 I at 2379-81.

B.[3723] 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%.[3724] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[3725]

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 levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased

[3723] *Id.; See also*, Westphal at 918.

[3724] *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

[3725] *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 [cholesteryl 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.)"

VLDL particle conversion.[3726] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[3727] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '920 patent are inherent to the compound when administered to a human subject."[3728] Inherency may not supply a missing claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[3729] Obviousness is based on what is *known* in the art at the time of the

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[3726] Bays May 16, 2011 Decl., ¶ 11 (noting the "general knowledge in the art that omega-3 fatty acids as a class increase LDL-C" in very-high TG patients); McKenney 2007, at 724 ("Because of the increase in LDL levels 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.").

[3727] Bays 2008 I at 400-402.

[3728] Defendants' Joint Invalidity Contentions at 400.

[3729] *See, e.g.*, *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) ("A party must . . . 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).

invention.[3730] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[3731] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

Defendants argue that the claims of the '920 patent which contain "a limiting clause, such as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively recited and therefore are not elements.[3732] This is incorrect. "There is nothing inherently wrong with defining some part of an invention in functional terms."[3733] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[3734] The claim term "to effect" acts as a positive limitation if the term represents "unexpected and improved effects of administration of the claimed compound."[3735] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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[3730] *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.").

[3731] *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

[3732] Defendants' Joint Invalidity Contentions at 401.

[3733] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

[3734] *Hoffer v. Microsoft Corp*., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

[3735] *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).

requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

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

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

(1) WO '118

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '920 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), WO '118 does not disclose or suggest a subject with the recited very high TG levels. WO '118 also does

not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. WO '118 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(2) WO '900

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '900 disclose or suggest elements of the '920 Claims. The cited portions of WO '900 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. The cited portions of WO '900 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

dosage or administration period. WO '900 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim 5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(3) Contacos

Contacos describes a study designed to determine the safety and efficacy of a statin (pravastatin) combined with fish oil either alone or in combination, for the management of patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '920 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Contacos further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(4) Grimsgaard

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of '920 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels.

The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG levels. Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. Grimsgaard further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(5) Hayashi

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

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '920 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject

had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Hayashi further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(6) Katayama

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '920 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels.

The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Katayama further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Katayama further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(7) Leigh-Firbank

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '920 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration

period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference does not disclose or suggest the subject having the recited baseline LDL-C level. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(8) Lovaza PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '920 Claims. The cited portions of the Lovaza PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza PDR further do not disclose or suggest the claimed

pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Lovaza PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(9) Maki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '920 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG level. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Maki further do

not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Maki further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claim 2, this reference does not disclose or suggest administration of the claimed pharmaceutical composition to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(10) Matsuzawa

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Matsuzawa disclose or suggest elements of the '920 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG level. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they

do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Matsuzawa further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 of the '920 Patent (and therefore all asserted claims), Matsuzawa does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Matsuzawa further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the claimed TG level.

(11) Mori 2000

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of Claims XX. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest administration

of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 further does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. Mori 2000 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(12) Mori 2006

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '920 Claims. The cited portions of Mori 2006 do not disclose or suggest these elements at least because they do not disclose or suggest administration

of EPA with the recited purity to a subject with the recited very high TG level. The cited portions of Mori 2006 further do not disclose or suggest administration of the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period to the subject with the claimed TG level. The cited portions of Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Mori 2006 also does not disclose or suggest administration of the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period to the subject with the claimed TG level. Mori 2006 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim 5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '920 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '920 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not

disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Nozaki further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(14) Omacor PDR

The Omacor PDR is the Physicians' Desk Reference describing Omacor.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '920 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Omacor PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in TG. With respect to Claims 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '920 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of Satoh further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. Satoh further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to

disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(16) Shinozaki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '920 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claim 1 of the '920 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. Shinozaki further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim

5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '920 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG level. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 of the '920 Patent (and therefore all asserted claims), Takaku does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Takaku further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level.

Further, with respect to Claim 4, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claim 5, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited reduction in TG in the subject with the claimed TG level. With respect to Claims 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '920 patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Facts supporting the non-obviousness of the claims of the '920 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '920 patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claims of the '920 patent Would Have Been Obvious

(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 '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."[3736] 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.[3737, 3738] Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent

[3736] Defendants' Joint Invalidity Contentions at 379.

[3737] 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, Mataki, 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 Invalidity Contentions at 394.

[3738] 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 Invalidity Contentions at 392-93.

reason" to combine must find a basis in the factual record.[3739] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3740] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3741] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil,

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[3739] *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).

[3740] *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").

[3741] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claims of the '920 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3742]

The analysis of the independent claim of the '920 patent is incorporated into all asserted claims that depend from that claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '920 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies

[3742] *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").

were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.[3743] As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-high or high TG patients, was expected. At the priority date of the '920 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[3744] This is an incorrect characterization

[3743] *See* Grimsgaard at 652 (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.)

[3744] Defendants' Joint Invalidity Contentions at 394-95.

of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[3745] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference

[3745] Defendants' Joint Invalidity Contentions at 394-95.

disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[3746] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[3747]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3748] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[3749] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[3750] Katayama does not disclose *any* LDL-C related

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[3746] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI_2 and PGI_3 Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[3747] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[3748] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[3749] Defendants' Joint Invalidity Contentions at 395 and 396.

[3750] Katayama at 2.

data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[3751] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[3752] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[3753] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

[3751] *Id.* at 16.

[3752] Defendants' Joint Invalidity Contentions at 394 and 395.

[3753] Matsuzawa at 7 and 19.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[3754] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[3755] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[3756] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

[3754] *Id.* at 23.

[3755] *Id.* at 10.

[3756] *Id.* at 11.

triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[3757] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[3758] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '920 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '920 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain

[3757] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

[3758] *See, e.g.*, Rambjor.

why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[3759] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[3759] Nozaki at 256.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[3760] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3761] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

[3760] Hayashi at 26, Table I.

[3761] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

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

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[3762] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)

[3762] Defendants' Joint Invalidity Contentions at 398.

would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[3763] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[3764] and DHA

[3763] Mori 2006 at 96.

[3764] Leigh-Firbank at 440.

is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[3765] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "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."[3766] Although teaching away is fact-dependent, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[3767]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[3768] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[3769] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may

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[3765] *See, e.g.* Grimsgaard at 654.

[3766] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[3767] *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.").

[3768] Mori 2000 at 1092.

[3769] Mori 2000 at 1088.

be favorable."[3770] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3771] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '920 patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or

[3770] Mori 2000 at 1092.

[3771] *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 '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."[3772] 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.[3773] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3774] Defendants' contentions are no more than an assertion that certain

[3772] Defendants' Joint Invalidity Contentions at 395.

[3773] *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).

[3774] *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").

claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3775] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '920 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3776]

The analysis of the independent claims of the '920 patent is incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to

[3775] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3776] *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").

Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '920 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.H.3.c.1.a.i.a.i, incorporated herein by reference, Katayama and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[3777] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

[3777] Defendants' Joint Invalidity Contentions at 398.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[3778] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[3779] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in 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."[3780] 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

[3778] Defendants state in their Joint Invalidity 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).

[3779] Grimsgaard at 654.

[3780] Defendants' Joint Invalidity 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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P[1]	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[3]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[3781] 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."[3782] 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

[3781] Grimsgaard at 657.

[3782] Grimsgaard at 654.

it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard 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." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[3783] A person of ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[3784] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[3785] based on long-term administration.[3786]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a

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[3783] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to 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.

[3784] Defendants' Joint Invalidity Contentions at 395.

[3785] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[3786] Takaku at ICOSAPENT_DFNDT00006834.

conclusion "only from the results of the present study."[3787] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[3788]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[3789] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[3790] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[3791] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other

[3787] Takaku at ICOSAPENT_DFNDT00006897.

[3788] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[3789] Takaku at ICOSAPENT_DFNDT00006884.

[3790] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[3791] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

times.[3792] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[3793]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[3794] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[3795] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '920 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

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[3792] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[3793] Takaku at ICOSAPENT_DFNDT00006897.

[3794] Takaku at ICOSAPENT_DFNDT00006897.

[3795] *See, e.g.*, Rambjor.

claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[3796] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person

[3796] Nozaki at 256.

of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[3797] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3798] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Further, Defendants have failed to offer a purported combination of references as part of their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any

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[3797] Hayashi at 26, Table I.

[3798] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

motivation to combine Nozaki and Hayashi with the other references of their purported obviousness combinations. Therefore, Defendants should be precluded from relying on these references.

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[3799] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or Maki —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would

[3799] Defendants' Joint Invalidity Contentions at 398.

not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[3800] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[3801] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with below-average levels of HDL-C levels.[3802] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated, monounsaturated and polyunsaturated fatty acids.[3803] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[3804] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have also contributed to the elevation in LDL cholesterol."[3805] Further, Maki admits that the

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[3800] Defendants' Joint Invalidity Contentions at 395.

[3801] Defendants' Joint Invalidity Contentions at 398.

[3802] Maki at 190.

[3803] Maki at 191.

[3804] Maki at 195.

[3805] 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).

"mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[3806] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Defendants mischaracterize the rise in LDL-C associated with the administration of omega-3 fatty acids as being a "negative effect" because they incorrectly focus on only the LDL-C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in LDL-C to be troublesome; Maki states that "the lack of increase in the total/HDL cholesterol ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level less worrisome."[3807] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[3808]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3809] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

[3806] Maki at 197.

[3807] Maki at 197.

[3808] Maki at 197.

[3809] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

(iii) The '920 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or in View of Satoh or Shinozaki in Further View of Contacos

With respect to the '920 patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[3810] Defendants also present charts purporting to assert that an additional 60 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 60 separate references, they additionally do not suggest any identify 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.[3811] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3812] Defendants' contentions are no more than an assertion

[3810] Defendants' Joint Invalidity Contentions at 395.

[3811] *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).

[3812] *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").

that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3813] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference would cause a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels.

Defendants formulate an obviousness argument that relies on Contacos.[3814] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim element or an "apparent reason" or motivation to combine the elements in the manner claimed,[3815].

[3813] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3814] *Id.*

[3815] *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).

Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore, Contacos fails to provide motivation to administer purified EPA to a very high TG patient population. Contacos also fails to provide motivation to administer purified EPA to a very high TG patient population.

The proposed combinations do not render the independent claims of the '920 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3816]

The analysis of the independent claims of the '920 patent is incorporated into all asserted claims that depend from those Claims.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '920 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama, Satoh and/or Shinozaki Do Not Disclose Purported Known Clinical

[3816] *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").

Benefits of Administering Pure EPA

Defendants rely on Katayama, Satoh and/or Shinozaki to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.H.3.c.1.a.i.a.i, incorporated herein by reference, Katayama merely confirms the safety of long term treatment of Epadel and its ability to lower both serum total 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 suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when compared to baseline, there was no significant effect when compared to placebo.[3817] Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[3818] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially

[3817] Satoh at 145.

[3818] Defendants' Joint Invalidity Contentions at 395 and 396.

increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population.

Further, Satoh was a small study conducted in only Japanese patients. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[3819] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[3820] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[3821] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis

[3819] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[3820] Defendants' Joint Invalidity Contentions at 395 and 396.

[3821] Shinozaki at 107-109.

upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[3822] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki and/or Contacos.

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[3823] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement do not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels, respectively. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or Kelley—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were

[3822] *See, e.g.*, Rambjor.

[3823] Defendants' Joint Invalidity Contentions at 398.

considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

Defendants rely on Geppert and/or Kelley to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[3824] Both Geppert and Kelley administer DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids. Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[3825] For example, Defendants' own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.[3826]

In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[3827] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.

[3824] Defendants' Joint Invalidity Contentions at 396.

[3825] *See* Mori 2006 at 96.

[3826] Maki at 197.

[3827] Geppert at 784.

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA was the only component of fish oil to increase LDL-C. For example, there is no data comparing DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying explain the mechanism of LDL-C increase.[3828] A person of ordinary skill would have not expected that EPA and DHA would have different effects on LDL-C based on Geppert.

Defendants contend that Kelley shows that DHA was responsible for the increase in LDL-C.[3829] In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[3830] Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in context with the other lipid effects reported in the study. Kelley states that:

> DHA supplementation may lower the risk of CVD by reducing plasma triacylglycerols; triaclyglycerol:HDL; the number of small, dense LDL particles; and mean diameter of VLDL particles. An increase was observed in fasting LDL cholesterol, but it is unlikely this increase is detrimental because no increase was observed in the overall number of LDL particles; actually, there was an 11% reduction that was statistically not significant. The reason LDL cholesterol increased despite no change in LDL particle number was that the LDL particles were made larger and hence more cholesterol rich by DHA treatment.[3831]

[3828] *Id*.

[3829] Defendants' Joint Invalidity Contentions at 396.

[3830] Kelley at 329.

[3831] Kelley at 329

Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. 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."[3832] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with 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 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy, including administration of DHA. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

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

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3833] As is the case with Kelley, Defendants use

[3832] Kelley at 324, 332.

[3833] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

hindsight to characterize a reference based on LDL-C levels alone without considering the other lipid effects studied, considered and reported.[3834] The isolated manner in which Defendants select such data points is not the approach that a person of ordinary skill would have taken at the time of the invention. Defendants' approach represents the use of impermissible hindsight bias. A person of ordinary skill would take into consideration the entire disclosure of a reference, including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a favorable effect in hypertriglyceridemic patients.

Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3835] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert and/or Kelley.

(iv) A Person of Ordinary Skill Would Not Have Been Motivated to Find an Omega-3 Fatty Acid "therapy that would reduce TG levels in patients with TG levels ≥500 mg/dL without negatively impacting LDL-C levels."

Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there

[3834] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation 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.").

[3835] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[3836] Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[3837] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[3838] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[3839] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

[3836] *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).

[3837] 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");

[3838] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[3839] *See Id.*, ¶ 17

In any event, a person of ordinary skill in the art 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. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[3840]	-20%	+45%
Lovaza/Omacor[3841]	-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 the lack of motivation.

Defendants offer no "apparent reason" to administer EPA as claimed to patients with fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on Lovaza/Omacor as the starting point to "find a therapy that would reduce TG levels in patients

[3840] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3841] Chan 2002 I at 2381 (Table 3).

with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels."[3842] Ironically, Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500 mg/dL but significantly increases LDL-C--an effect understood to be a consequence of TG reduction and the increased conversion of VLDL to LDL particles.[3843]

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[3844] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[3845] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels

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[3842] Defendants' Joint Invalidity Contentions at 397.

[3843] *See* Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that "[t]hese 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

[3844] 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")

[3845] 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)

the most in patients with the highest pretreatment TG levels.[3846] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-C was often offset by concurrent treatment with statins.[3847] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[3848]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[3849] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[3850]

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[3851] Correspondingly, prescription

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[3846] *See* Bays 2008 Rx Omega-3 p. 402.

[3847] *See* Harris 2008 at 14, McKenney at 722.

[3848] McKenney at 722-23.

[3849] *See* Westphal at 918, Harris 1997 at 389.

[3850] *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 chancing 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 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)").

[3851] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[3852] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the number of small, dense LDL particles to larger LDL particles.[3853] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[3854] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[3855]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[3856] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to

[3852] McKenney 2007 at 722 (*see* Fig. 1).

[3853] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[3854] Stalenhoef at 134.

[3855] Harris 1997 at 389.

[3856] Defendants' Joint Invalidity Contentions at 397.

increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[3857] (which is a reflection of total atherogenic lipoproteins)[3858] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention.[3859] Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the

[3857] *see* Section V.O.

[3858] *see* Section III.

[3859] *See, e.g.*, Defendants' Joint Invalidity Contentions at 392.

combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population,[3860] they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill would have understood these patient populations to be distinct with different impacts of lipid therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would not have considered the dosage modification suggested by defendants to be routine; Defendants' argument to the contrary represents hindsight bias.

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

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

(i) The '920 Patent is not Obvious Over WO '118 or WO '900, in Combination with the Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '920 patent, Defendants present a combination of five references: "WO '118 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."[3861] Defendants also present charts arguing 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

[3860] Defendants' Joint Invalidity Contentions at 399-400.

[3861] Defendants' Joint Invalidity Contentions at 402.

would combine 61 separate references, they additionally do not identify any motivation for combining these references.[3862, 3863] 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.[3864] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3865] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other

[3862] Defendants' bare assertion that the asserted claims are obvious "in view of one or more of the references cited in Sections II and V.A and B, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, 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 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.

[3863] 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 Invalidity Contentions at 392-93.

[3864] *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) (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 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).

[3865] *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").

disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3866] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[3867] Contrary to Defendants' assertion that WO '118 discloses "the administration of 4 g of pure EPA with no DHA,"[3868] WO '118 fails to disclose the claimed subject with the specified very high TG levels (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[3869]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[3870] WO

[3866] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3867] WO '118 at 9.

[3868] Defendants' Joint Invalidity Contentions at 402.

[3869] WO '118 at 22-23.

[3870] WO '118 at 8.

'118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[3871]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[3872] WO '118 states that "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[3873] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[3874] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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

[3871] *See* Section III.

[3872] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

[3873] WO '118 at 22-23.

[3874] WO '118 at 23.

WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[3875] Moreover, WO '900 does not teach the desired effect of EPA other than commenting generally that it "may promote health and ameliorate or even reverse the effects of a range of common diseases."[3876] It has no discussion, for example, on any TG-lowering effect of EPA. Although WO '900 identifies DHA as an "undesired molecule", it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than commenting generally that "the desired effects of EPA may be limited or reversed" by them.[3877] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claims of the '920 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3878]

The analysis of the independent claims of the '920 patent is incorporated into all asserted claims that depend from those Claims.

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge

[3875] *See, e.g.*, '900 Pub. at 16-17.

[3876] '900 Pub. at 5.

[3877] '900 Pub. at 39.

[3878] *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").

that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[3879]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. 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.[3880] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3881] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

[3879] Defendants' Joint Invalidity Contentions at 402.

[3880] *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).

[3881] *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").

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

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3882] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '920 patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in

[3882] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

View of Katayama, Matsuzawa and/or Takaku.

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."[3883] 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.[3884] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3885] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

[3883] Defendants' Joint Invalidity Contentions at 402.

[3884] *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).

[3885] *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").

Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3886] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[3887] 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

[3886] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3887] Defendants' Joint Invalidity Contentions at 402.

record.[3888] Defendants' assertions related to motivation are insufficient,[3889] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed.[3890] Therefore, Defendants should be precluded from relying on this these references.

As discussed above in Section V.H.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population. As discussed above in Section

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[3888] *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).

[3889] 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.

[3890] *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).

V.H.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[3891] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[3892]

The proposed combination does not render the independent claims of the '920 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[3893]

The analysis of the independent claims of the '920 patent is incorporated into all asserted claims that depend from those Claims.

(a) Grimsgaard, Mori 2000 and/or Maki Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known

[3891] Takaku at ICOSAPENT_DFNDT00006897.

[3892] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[3893] *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").

regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[3894]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.H.3.c.1.a.ii.a.iii is incorporated herein by reference. A person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[3895] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[3896] However, one of ordinary skill in the art

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[3894] Defendants' Joint Invalidity Contentions at 403.

[3895] 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.

[3896] Maki at 195.

knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[3897] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[3898] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[3899] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL.

A person of ordinary skill in the art 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,

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[3897] 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.").

[3898] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[3899] Defendants' Joint Invalidity Contentions at 215.

as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate[3900]	-20%	+45%
Lovaza/Omacor[3901]	-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."[3902] Both of the "reasons" identified by Defendants are false.

[3900] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[3901] Chan 2002 I at 2381 (Table 3).

[3902] Defendants' Joint Invalidity Contentions at 404.

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.[3903] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald do *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not." First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[3904] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with other saturated and polyunsaturated fatty acids.[3905] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[3906] Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[3907] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel

[3903] 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.

[3904] The discussion related to Leigh-Firbank in Section V.H.3.c.1.a.i.a.iii is incorporated herein by reference.

[3905] The discussion related to Kelley in Section V.H.3.c.1.a.iii.a.ii is incorporated herein by reference.

[3906] *See* Mori 2006 at 96.

[3907] Kelley at 329.

increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[3908] Finally, Theobald also does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid. Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[3909]Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[3910] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[3911] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients

[3908] 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.")

[3909] *See* Mori 2006 at 96.

[3910] Defendants' Joint Invalidity Contentions at 404.

[3911] Mori 2000 at 1092.

because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA," the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been well documented.[3912] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[3913] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[3914] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[3915]

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."[3916] As

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[3912] 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.

[3913] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[3914] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[3915] Harris 2008 at 13.

[3916] Defendants' Joint Invalidity Contentions at 404-405.

discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[3917]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that DHA is *more* cardioprotective than EPA.[3918] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[3919] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[3920] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[3921] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA *and* DHA were known to have cardioprotective effects, and there were studies suggesting DHA was *more* cardioprotective than EPA.

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to

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[3917] 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").

[3918] Harris 2007 at 8.

[3919] *Id.*

[3920] 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.").

[3921] *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 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.").

patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[3922] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[3923]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[3924] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[3925] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG levels > 500 mg/dL."[3926],[3927] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of

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[3922] Defendants' Joint Invalidity Contentions at 405-406.

[3923] Defendants' Joint Invalidity Contentions at 406.

[3924] *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.").

[3925] Nakamura, Matsuzawa, and Takaku.

[3926] Defendants' Joint Invalidity Contentions at 405.

[3927] 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.

ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one patient had a baseline TG level > 500 mg/dL.[3928] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[3929] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[3930] Based on this disclosure, only one patient definitively had a baseline TG level ≥ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[3931] In Takaku, three patients had baseline TG levels above 500 mg/dL.[3932] However, the mean baseline TG level for all patients was 245 mg/dL.[3933] Indeed, the mean baseline TG level of the patients in all three studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[3934] Defendants have failed to identify all of the claimed elements and fail to provide motivation to

[3928] Nakamura at 23, Table 1.

[3929] Nakamura at 23, Tables 1 and 2.

[3930] *Id.* at 23.

[3931] *Id.* at 10.

[3932] Takaku at ICOSAPENT_DFNDTS00006895.

[3933] Takaku at ICOSAPENT_DFNDTS00006875.

[3934] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[3935] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[3936] In fact, Defendants acknowledge in their Joint Invalidity Contentions that "DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[3937] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[3938] Therefore, a person of ordinary skill would not have

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[3935] Defendants' Joint Invalidity Contentions at 406.

[3936] Mori 2006 at 98.

[3937] Defendants' Joint Invalidity Contentions at 407.

[3938] 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 grater with DHA supplementation than EPA supplementation).

been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[3939] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[3940] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia, because these studies were not designed to determine the effect of dose on the degree of TG reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

[3939] Defendants' Joint Invalidity Contentions at 406.

[3940] Defendants' Joint Invalidity Contentions at 406-07.

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[3941] Therefore, a person of ordinary skill would not have been motivated to administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito treated subjects having baseline triglyceride levels greater than 500 mg/dl."[3942] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy." Defendants first support this argument by asserting that a person of ordinary skill in the art would have known

[3941] *See* Section III.

[3942] Defendants' Joint Invalidity Contentions at 407.

that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition, however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[3943]

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

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided." While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[3944]

Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in

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[3943] *See* Section IV.

[3944] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese 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.

LDL-C with DHA." However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[3945] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[3946] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[3947] (which is a reflection of total atherogenic lipoproteins)[3948] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

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

[3945] 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").

[3946] Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

[3947] *see* Section V.O.

[3948] *see* Section III.

(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

combined to teach the administration of the claimed EPA to very high TG patients.[3949] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3950] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3951]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3952]

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended

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[3949] *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").

[3950] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3951] *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").

[3952] *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)).

purpose.[3953] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(b) Defendants Have Not Shown that Claim 3 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 3.

Defendants contend, without providing meaningful support, that the claim element was well known in the art. 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. Defendants make a conclusory statement that the claimed method of

[3953] *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.")

treatment was well known in the art, but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3954] Further Defendants cite to the "Lovaza product" without identifying the prior art reference to which they refer. Such a reference is inadequate.

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3955] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(c) Defendants Have Not Shown that Claim 4 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 4.

Defendants contend that it would be obvious that a person receiving the claimed EPA compositions would have a fasting baseline LDL-C from 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL because hypertriglyceridemic patients in the Lovaza label had a mean LDL-C level of 100 mg/dL. Plaintiffs note that Defendants fail to provide specific arguments for

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[3954] *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)).

[3955] *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.")

the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. These contentions: 1) 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 2) 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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Further, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements, other than stating that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would benefit from receiving the claimed fish oil treatment. Defendants also state erroneously that a patient with LDL-C levels of 50 mg/dL to about 150 mg/dL or 50 mg/dL to about 300 mg/dL would be considered hypertriglyceridemic. Plaintiffs note that Defendants fail to provide specific arguments for the claimed LDL-C range of 40 mg/dL to about 115 mg/dL. Defendants do not establish that a person of ordinary skill would have been motivated to combine the elements to achieve the claimed invention.[3956]

[3956] *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)).

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[3957] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(d) Defendants Have Not Shown that Claim 5 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 5.

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.[3958] 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

[3957] *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.")

[3958] *Id.*

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. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be combined.[3959] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[3960] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each prior art reference as a whole.[3961] Each reference must be evaluated for all that it teaches. Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3962]

[3959] *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").

[3960] *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").

[3961] *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).

[3962] *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").

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed methods of treatment, without providing a reason that would have prompted a person of ordinary skill to combine the elements.[3963] Such a naked assertion does not show why a person of ordinary skill would have been motivated to treat the recited patient population using the claimed methods of treatment.[3964]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[3965] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

[3963] *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)

[3964] *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)).

[3965] *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.")

(e) Defendants Have Not Shown that Claims 6 and 7 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 Claims 6 and 7.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[3966] 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.

[3966] 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.

Defendants further contend, without support, that a person of ordinary skill would "reasonably expect to see the same hypotriglyceridemic effect from a pure EPA formulation containing no DHA," as a formulation containing both EPA and DHA. Defendants conclude, without support, that it would have been obvious to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing triglycerides while avoiding an increase in LDL. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) 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 3) 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 do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[3967] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[3968] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a

[3967] *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").

[3968] *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").

whole. Each reference, however, must be evaluated for all that it teaches.[3969] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3970]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[3971] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[3972] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in

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[3969] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3970] *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").

[3971] *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)).

[3972] 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).

achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[3973] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[3974]

(f) Defendants Have Not Shown that Claim 8 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 8.

Defendants offer no reference in support of their contention that this claims is obvious. Defendants contend, without providing any support, that it would be obvious to one of skill in the art to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels. 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*

[3973] *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).

[3974] *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.").

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 combined to teach the administration of the claimed EPA to very high TG patients.[3975] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[3976] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[3977]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment would have been obvious but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[3978]

[3975] *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").

[3976] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[3977] *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").

[3978] *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

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[3979] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

Defendants rely on only one reference in their invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that "it was known that Apo-B is a component of LDL-C." Defendants cite to no passage or page of Theobald in connection with that argument and no support for their argument that Theobald makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all atherogenic lipoproteins.[3980]

Defendants then make the unsupported assertion that "one of ordinary skill in the art would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL syntheses." They are incorrect. Neither Defendants' characterization of Theobald nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render this claim obvious. Defendants' assertion that EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL

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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)).

[3979] *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.")

[3980] June 26, 2012 Bays Declaration; *see also* Section III.

synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with respect to this claim or Apo-B levels.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Crypthecodinium 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:[3981]

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

	DHA		Placebo		
	Before treatment	After treatment	Before treatment	After treatment	Treatment effect[1]
Total cholesterol (mmol/L)	5.15 ± 0.145[2]	5.44 ± 0.174	5.08 ± 0.168	5.22 ± 0.155	0.22 (0.01, 0.42)[3]
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)[4]
HDL cholesterol (mmol/L)[5]	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)[6]	1.03 ± 0.094	1.01 ± 0.089	1.06 ± 0.106	1.19 ± 0.103	−0.18 (−0.37, 0.05)
Apolipoprotein B (g/L)	0.84 ± 0.027	0.87 ± 0.026	0.83 ± 0.028	0.84 ± 0.028	0.03 (0.002, 0.055)[7]
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)[3]
Weight (kg)[8]	70.1 ± 2.04	70.6 ± 2.06	70.5 ± 2.01	70.6 ± 2.01	0 (−0.85, 0.24)

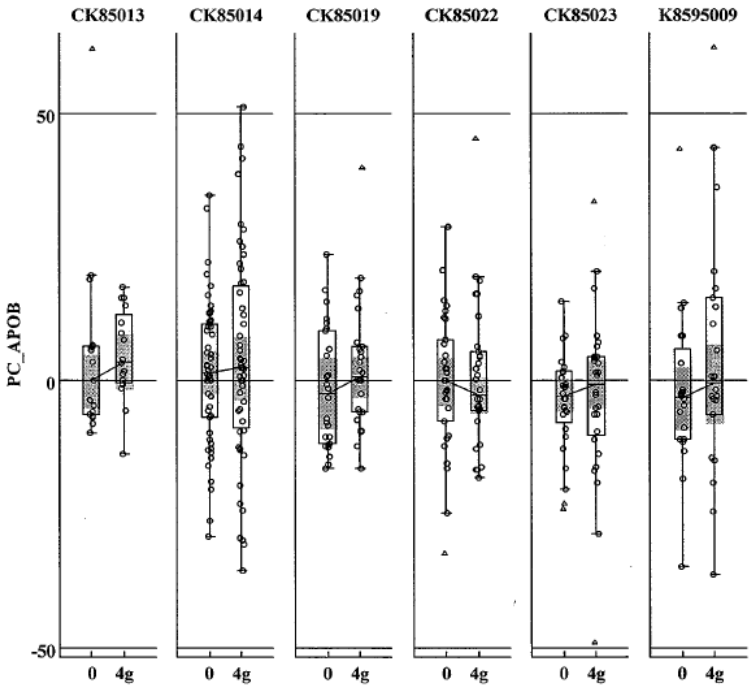
[1] Mean difference between active treatment and placebo; 95% CI in parentheses.
[2] $\bar{x}$ ± SEM (all such values); $n = 38$.
[3,4,7] Paired t test: [3] $P = 0.04$, [4] $P = 0.004$, [7] $P = 0.03$.
[5] HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.
[6] $n = 37$; data were log transformed before analysis by paired t test.
[8] Weight increased over the entire study period. Significant order × 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.

[3981] Theobald at 561, table 3.

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 Apo-B levels in patients with very high TG levels.[3982] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[3983]

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,[3984] there was no change in Apo-B between the control and treatment groups.

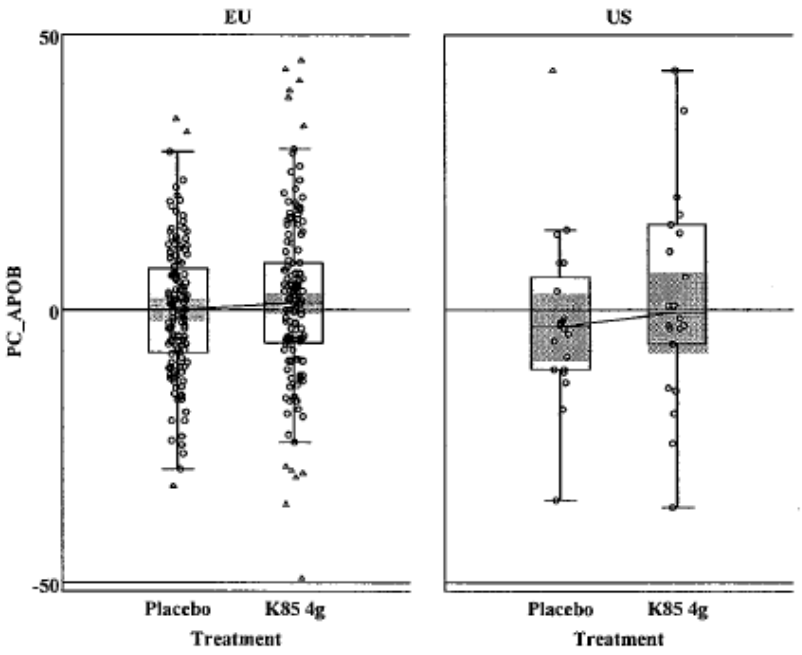
[3982] May 8, 2012 Bays Declaration.

[3983] Lovaza Approval Package at Table 14.

[3984] The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

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.[3985]

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.[3986] 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,

[3985] Lovaza Approval Package at Table 7.

[3986] *See* Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

agreed that the Apo-B effects reported by the claimed inventions were unexpected in light of those references, also reflecting a lack of motivation and no reasonable expectation of success.[3987]

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[3988] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[3989] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

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

[3987] Defendants' Contentions at 236.

[3988] ATP-III at 3170; Bays 2008 I at 395.

[3989] Kwiterovich in Kwiterovich at 4.

(g) Defendants Have Not Shown that Claim 9 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 9.

Defendants contend that it would have been obvious to use the claimed composition to reduce VLDL-C levels, and that the recited VLDL-C reduction represents therapeutic efficacy. 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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[3990] As such, Defendants fail

[3990] *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,

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

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

(h) Defendants Have Not Shown that Claim 10 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 10. Defendants also assert that "one of skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in LDL-C with DHA with a reasonable expectation of success." As discussed above, these contentions are incorrect and contrary to what a person of ordinary skill would expect. Moreover, 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

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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)).

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 do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[3991] As such, Defendants fail to demonstrate that there was no motivation to combine the references to achieve the claimed invention.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make conclusory statements without providing any support. What is more, Defendants do not even discuss the reasonable expectation of reducing

[3991] *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)).

LDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of reducing LDL-C levels using the claimed methods.

Defendants further allege that the effects on LDL-C represent "properties inherent upon administering a formulation known in or rendered obvious by the prior art." Defendants do not identify any prior art that shows that the effects on LDL-C was an inherent property of a pure EPA composition. Moreover, any inherent property that was not readily known in the art may not show obviousness because "[t]hat which may be inherent is not necessarily known; [and] obviousness cannot be predicated on what is unknown."[3992]

4. The '920 Patent is Not Invalid Under § 112

a) Defendants Have Not Demonstrated that the Claims of the '920 patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[3993] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the art about the scope of the invention" in light of the specification and the prosecution history.[3994] The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[3995]

[3992] *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993).

[3993] 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 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.

[3994] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

[3995] *Id.* at 2129.

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[3996] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[3997] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[3998] Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

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

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[3996] *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) ("Claim language employing terms of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the context of the invention."); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir. 2003) ("The question becomes whether one of ordinary skill in the art would understand what is claimed when the claim is read in light of the specification.") (discussing the term "about"); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d 1116, 1120 (Fed. Cir. 2002) ("It is well established that when the term 'substantially' serves reasonably to describe the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish the claimed subject matter from the prior art, it is not indefinite.").

[3997] *See, e.g.*, *Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim 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).

[3998] *See generally* the '920 patent and its prosecution history.

is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[3999] In light of the specification and prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[4000] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants further allege that the term "compared to baseline" is indefinite. Defendants, again, provide no basis for this allegation. In light of the specification and the prosecution history, a person of ordinary skill would know with reasonable certainty the scope of the term "compared to baseline" and therefore does not render the claims indefinite.[4001]

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an

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[3999] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. 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, 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").

[4000] *See generally* the '920 patent and its prosecution history.

[4001] *See generally* the '920 patent and its prosecution history.

infringement of such patent."[4002] Plaintiffs assert that Defendants' ANDA products will be used in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '920 patent claims are not indefinite for improperly mixing methods and formulations.

b) Defendants Have Not Demonstrated that the Claims of the '920 patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" that the applicant "invented" or "had possession" of the claimed subject matter when the application was filed.[4003] Support need not be literal[4004]—it may be implicit[4005] or inherent[4006] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[4007]

Defendants make three arguments regarding the written description requirement. First, Defendants contend that elements reciting the baseline TG levels of the asserted claims lack written description. This is incorrect. The specification of asserted patents literally discloses the

[4002] 35 U.S.C. § 271(c) (emphasis added).

[4003] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[4004] *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).

[4005] *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.

[4006] *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

[4007] *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.

claimed invention.[4008] Moreover, the recited baseline TG levels of the claimed invention appear in the original claims of the application to which the asserted patent claims priority. Thus, there is a strong presumption that the claimed invention is adequately described.[4009] Defendants do not and cannot rebut this presumption. Specifically, the patient population is originally claimed as "a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl."[4010] The asserted claims recite the same patient population. Defendants do not contend that the patient population of the asserted claims is not literally described by the specification and in the original claims of the application to which the asserted patent claims priority. In fact, the specification and the provisional patent application claims at the time of filing described these limitations.[4011] Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the dosages and quantities of the claimed methods.[4012] Moreover, the dosages and quantities of the

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[4008] *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."); *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.").

[4009] *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").

[4010] *See* U.S. Application No. 12/702,889.

[4011] See e.g., '920 patent at 13:29-34; 14:49-51; U.S. Application No. 12/702,889.

[4012] *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.");

method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[4013] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[4014] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against a second subject or against a second population." The specification demonstrates that the applicants were in possession of the claimed inventions. For example, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a comparison of a subject or a population against a second subject, baseline, or a second population.

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.").

[4013] *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").

[4014] *See* U.S. Provisional Application No. 61/151,291.

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[4015] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[4016] Written description requires only that the specification reasonably conveys that the applicant had possession of the claimed subject matter when the application was filed. Therefore, whether the claims are obvious has no bearing on the adequacy of written description.

c) Defendants Have Not Demonstrated that the Claims of the '920 patent Are Invalid for Lack of Enablement

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

[4015] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

[4016] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is 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 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.").

Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[4017] The enablement requirement is separate and distinct from the written description requirement,[4018] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[4019]

Defendants make two specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary skill would be able to determine the amounts of the components in the pharmaceutical composition without any experimentation, much less undue experimentation.

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The

[4017] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[4018] *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[4019] MPEP § 2164.

clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[4020] Therefore, the claims are not invalid for lack of enablement.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '920 patent's specification enables a person of ordinary skill to obtain the claimed limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.H.3. Furthermore, Plaintiffs have initiated human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its claimed methods.[4021, 4022] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

I. The '560 Patent

1. The '560 Patent Claims Eligible Subject Matter Under § 101

[4020] *See* VASCEPA® Prescribing Information at Table 2.

[4021] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical 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.").

[4022] *See* May 16, 2011 Bays Declaration at Appendix B.

Defendants' allegation that the asserted claims of the '560 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[4023] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '560 patent does not meet this requirement and thwarts the purpose of the Rules.[4024]

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical phenomenon, or abstract idea.[4025] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[4026]

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '560 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and]

[4023] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[4024] 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 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).

[4025] *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) ("First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts.").

[4026] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[4027] However, the claims merely recited this natural law without reciting any novel application of it.[4028] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[4029] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[4030]

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions make clear that EPA of the requisite purity and characteristics is not found in nature.[4031] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their natural state are patent-eligible.[4032] Moreover, Defendants' assertions are immaterial to a Section

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[4027] *Mayo*, 132 S. Ct. at 1294.

[4028] *Id.* at 1301.

[4029] *Id.*

[4030] *Id.* at 1302 (contrasting the patent-ineligible claims of that case to "a typical patent on a new drug or a new way 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).

[4031] *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).

[4032] *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).

101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[4033]

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[4034] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[4035] To say that the claims of the '560 patent claim a law of nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to underlying principles of nature" that would "make all inventions unpatentable."[4036] Indeed, even those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[4037]

[4033] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

[4034] *See* Defendants' Joint Invalidity Contentions at 567.

[4035] See *CellzDirect*, 827 F.3d at 1048-49 ("The [asserted] claims are like thousands of others that recite processes 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).").

[4036] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

[4037] *See Mayo*, 132 S. Ct. at 1034 ("Prometheus, supported by several *amici*, argues that a principle of law denying patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research.").

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '560 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[4038] As discussed above, the asserted claims of the '560 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[4039]

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In addition, as discussed above, the asserted claims are not merely a naturally-occurring phenomena, and thus satisfy the requirements of § 101.

2. The Asserted Claims of the '560 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[4040] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as

[4038] *See Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

[4039] *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 "just one step in the whole process" claimed by the invention).

[4040] *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

is contained in the claim.[4041] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[4042] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[4043] In addition, public "possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[4044] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[4045] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[4046]

Defendants assert that Claims 1-20 of the '560 Patent are anticipated by the WO '118 reference.[4047]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference

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[4041] *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).

[4042] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[4043] *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).

[4044] *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).

[4045] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[4046] *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).

[4047] 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.

into Exhibit I, and vice-versa. WO '118 does not anticipate the claims of the '560 patent because it does not describe, properly arrange, or enable the '560 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '560 Patent

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

It is well established that, for a prior art reference to anticipate, "every element of the claimed invention must be identically shown in a single reference."[4048] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[4049] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '560 Patent: *to effect a reduction in triglycerides in the subject.* WO '118 further entirely fails to disclose the following elements of Claim 11 of the '560 Patent: *to effect a reduction in triglycerides in the subject compared to placebo control.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[4050] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claims of the '560 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are

[4048] *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).

[4049] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

[4050] Defendants' Invalidity Contentions at 202-204.

entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[4051] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[4052] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[4053] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claims every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[4054] Rambjor is a clinical study which

[4051] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[4052] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[4053] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[4054] *See, e.g.*, Rambjor.

administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

Therefore, WO '118 cannot anticipate the independent claims of the '560 patent. Because the dependent claims include all of the claim elements of the independent claims, WO' 118 cannot anticipate any of the dependent claims as well.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[4055] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[4056]

The preamble of the asserted claims is limiting for several reasons. The term "subject" in the preamble of the independent claims defines and provides antecedent basis for the "subject"

[4055] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

[4056] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

recited in the body of the claims. When reading the claim, one must rely on both the preamble and the claim body to define the claimed invention.

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[4057] The recitation of a "method of reducing triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[4058] Thus, the entire preamble in the independent claims of the '560 must contain patentable weight.

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

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden

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[4057] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer 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").

[4058] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina."[4059] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[4060] WO '118 does not expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claims.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of the reference.[4061] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

There is no evidence in that subject as described in the claims were ever treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of the subject as described in the claims. It does not. Defendants' argument rests on the definition in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL." WO '118's definition is not tied to a specific subject and there are no working examples, data or other reference in WO '118 indicating that any subject with fasting TG levels of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as

[4059] WO '118 at 12.

[4060] *Id.*

[4061] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

evidence that a "person of ordinary skill in the art would have understood that the term 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable and then merely provides examples of commercially available "soft capsules," such as Omacor. The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[4062] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claims every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '560 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[4063] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[4064] and therefore

[4062] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[4063] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[4064] *Atofina*, 441 F.3d at 1000.

failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as compared to the patent's claimed range of 0.1 to 5.0 percent.[4065] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[4066] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[4067] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

[4065] *Id.*

[4066] *Id.*

[4067] *See* Section III.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[4068] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL), and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[4069] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[4070] Accordingly, in these populations, physicians focused on lowering LDL-C.[4071] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary treatment goal.[4072] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In

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[4068] *Id.*

[4069] ATP III at 3335; *See also* Section III.

[4070] *Id.*

[4071] *Id.*

[4072] *Id.*

fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claims of the '560 Patent.

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

WO '118 further does not anticipate the claims of the '560 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '560 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more 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 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less

one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[4073] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[4074] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[4075] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '560 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '560 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '560 patent and cannot anticipate the independent claims of the '560 Patent.

WO '118 further does not anticipate the claims of the '560 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a

[4073] *Atofina*, 441 F.3d at 1000.

[4074] *Id.*

[4075] *Id.*

portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[4076] Therefore, WO '118 discloses EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed generic range for the EPA composition in the claimed pharmaceutical composition.

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[4077] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[4078] and therefore failed to anticipate the claimed range.[4079] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[4080] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to

[4076] WO '118 at 22.

[4077] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[4078] *Atofina*, 441 F.3d at 1000.

[4079] *Atofina*, 441 F.3d at 1000.

[4080] *Id.*

anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[4081]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '560 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '560 patent. Therefore, WO '118's broad disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claims of the '560 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[4082] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '560 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between. There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claims of the '560 patent.

[4081] *Id.*

[4082] WO '118 at 22.

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

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

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

Defendants fail to address any of the claim elements of the dependent claims. Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any meaningful basis for concluding that WO '118 teaches these elements. Defendants further argue that "aspects of the claims relating to effects that are to be achieved by practicing the claimed method represent inherent, natural properties of EPA, and are entitled to no patentable weight." To the extent the recited claim elements relate to the administration step,

the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method, Defendants' contentions that the claim limitations are inherent properties of EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO '118, they fail to identify any basis, explanation, or even supporting argument for that assertion. Defendants have not met the burden to establish anticipation with the naked assertion that the effects are inherent, natural properties of EPA.

Further, Defendants entirely fail to prove that inherently discloses the recited claim limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[4083] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[4084] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[4085] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

[4083] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[4084] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[4085] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

3. The Claims of the '560 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '560 patent obvious.[4086] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '560 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of the '560 patent itself to guide its combination of references.[4087] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[4088]

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

- 1) ". . .the asserted claims of the '560 patent would have been obvious over 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."

- 2) ". . .the asserted claims of the '560 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of

[4086] Defendants' Joint Invalidity Contentions at 13-25.

[4087] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention 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))).

[4088] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, 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 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.

administering purified 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."

- 3) ". . .the asserted claims of the '560 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '560 patent would have been obvious over WO '118 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."

- 5) ". . . the asserted claims of the '560 patent would have been obvious over 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."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[4089] 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.[4090]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[4091] Indeed, any teaching in the art that points away from the claimed invention must be considered.[4092] A reference teaches away if a person of ordinary skill, upon reading the reference, would be

[4089] 35 U.S.C. § 103(a).

[4090] *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).

[4091] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[4092] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

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.[4093] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[4094]

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[4095] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[4096] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[4097]

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[4098] "[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."[4099] "This is so because inventions in most, if not all, instances rely upon building

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[4093] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[4094] *Id*.

[4095] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[4096] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[4097] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

[4098] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[4099] *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))

blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[4100]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[4101] or to modify a prior art reference in a way that "would destroy the fundamental characteristics of that reference."[4102] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[4103] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[4104] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[4105]

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[4106] and "a reasonable expectation of success."[4107]

[4100] *KSR*, 550 U.S. at 418-419.

[4101] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

[4102] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[4103] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[4104] *Id*. at 88.

[4105] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

[4106] *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).

[4107] *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).

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[4108] This protects against the use of hindsight to pick through the prior art based solely on structural similarity to the claimed compound.[4109] Any assertion of an "apparent reason" must find a basis in the factual record.[4110]

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[4111] including those discovered after the patent was filed or even issued.[4112] "The basic principle behind this rule is straight-forward—that which would

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[4108] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; 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).

[4109] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (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).

[4110] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[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*, 619 F.3d at 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 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").

[4111] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [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.").

[4112] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

have been surprising to a person of ordinary skill in a particular art would not have been obvious."[4113] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[4114]

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[4115] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[4116] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[4117] These factual inquiries "guard against slipping into use of hindsight,"[4118] and "may often be the most probative and cogent evidence of nonobviousness."[4119]

[4113] *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.").

[4114] *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.'").

[4115] *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).

[4116] *Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1569 (Fed. Cir. 1987).

[4117] *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.

[4118] *Graham*, 383 U.S. at 36.

[4119] *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)).

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[4120]

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

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying degrees of purity, in a wide range of doses and administration periods, to subjects who have baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[4121] Inconsistency in dosages and administration periods

[4120] *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.").

[4121] Mori 2006 at 96.

and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[4122] Defendants mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[4123] In addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower

[4122] Defendants' Joint Invalidity Contentions at 579 (*see* FN 106).

[4123] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 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).

TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[4124] Clinically, the authoritative guidance to physicians on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[4125]

Finally, from a therapeutic standpoint, a person of ordinary skill understood that the effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the

[4124] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

[4125] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG level of the patient receiving treatment.

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[4126] The fibrate, Tricor (fenofibrate), for example, decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[4127] and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[4128] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[4129] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[4130] Similar results were seen with the administration of Lopid (gemfibrozil).[4131] The differing effects of fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with

[4126] *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).

[4127] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[4128] *Id.*

[4129] *Id. See also*, Trilipix Label at 27.

[4130] *Id. See also*, Trilipix Label at 27.

[4131] *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).

normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	**Mean Baseline TG Value**	**TG**	**LDL-C**	**HDL-C**	**Total-C**
Tricor (fenofibrate)[4132]	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

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.[4133] It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.[4134] 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%.[4135] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[4136]

[4132] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[4133] Chan 2002 I at 2379-81.

[4134] *Id.; See also*, Westphal at 918.

[4135] *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

[4136] *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

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 levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[4137] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the

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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."); 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.)"

[4137] Bays May 16, 2011 Decl., ¶ 11 (noting the "general knowledge in the art that omega-3 fatty acids as a class increase LDL-C" in very-high TG patients); McKenney 2007, at 724 ("Because of the increase in LDL levels 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.").

highest baseline TG levels[4138] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '560 patent are inherent to the compound when administered to a human subject."[4139] Inherency may not supply a missing claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[4140] Obviousness is based on what is *known* in the art at the time of the invention.[4141] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[4142] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

[4138] Bays 2008 I at 400-402.

[4139] Defendants' Joint Invalidity Contentions at 579-80.

[4140] *See, e.g.*, *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) ("A party must . . . 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).

[4141] *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.").

[4142] *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

Defendants argue that the claims of the '560 patent which contain "a limiting clause, such as 'effects,' 'to effect' or 'is effective to,'" simply express the intended result of a process step positively recited and therefore are not elements.[4143] This is incorrect. "There is nothing inherently wrong with defining some part of an invention in functional terms."[4144] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[4145] The claim term "to effect" acts as a positive limitation if the term represents "unexpected and improved effects of administration of the claimed compound."[4146] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

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

Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent. Where a limitation is absent from any Independent Claim, that limitation is absent from all asserted claims, and that analysis is incorporated by reference into each dependent claim. For any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted claims is not a concession that such limitation is present in the reference. By discussing

[4143] Defendants' Joint Invalidity Contentions at 580.

[4144] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

[4145] *Hoffer v. Microsoft Corp*., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

[4146] *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).

Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants have appropriately divided the claim language for any purpose.

(1) WO '118

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '560 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), WO '118 does not disclose or suggest a subject with the recited very high TG level. WO '118 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or dosage. WO '118 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 11, WO '118 does not disclose or suggest a method to effect a reduction in TG in the subject based on a comparison to placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the

recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(2) WO '900

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '900 disclose or suggest elements of the '560 Claims. The cited portions of WO '900 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. The cited portions of WO '900 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. WO '900 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, WO '900 does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With

respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(3) Contacos

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '560 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Contacos further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect to effect the

recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Contacos does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction based on a comparison to a placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(4) Grimsgaard

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of the '560 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG level. Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited administration period. Grimsgaard further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Grimsgaard does not disclose or suggest a method to effect a reduction in TG in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-9 and 18-19, this reference fails to disclose or suggest the recited capsule dosage.

(5) Hayashi

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

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '560 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject

had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Hayashi further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Hayashi does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(6) Katay**a**ma

Katayama was directed to an investigation of the safety and efficacy of Epadel during long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,

Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '560 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Katayama further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Katayama further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Katayama does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in

the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(7) Leigh-Firbank

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '560 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Leigh-Firbank further do not disclose or suggest a method administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Leigh-Firbank does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction based on a comparison to a placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(8) Lovaza PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '560 Claims. The cited portions of the Lovaza PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a method administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The Lovaza PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to Claim 11, the Lovaza PDR does not disclose or

suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction based on a comparison to a placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(9) Maki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '560 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Maki further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

compositions, dosage, or administration period. Maki further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Maki does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction based on a comparison to a placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(10) Matsuzawa

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Matsuzawa disclose or suggest elements of the '560 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Matsuzawa further do not disclose or suggest a method of administering the claimed

pharmaceutical composition to effect to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Matsuzawa does not disclose or suggest a subject with the recited very high TG level. Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Matsuzawa further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Matsuzawa does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(11) Mori 2000

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of the '560 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest administration

of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. Mori 2000 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Mori 2000 does not disclose or suggest a method to effect a reduction in TG in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(12) Mori 2006

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '560 Claims. The cited portions of Mori 2006 do not

disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. The cited portions of Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. Mori 2006 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Mori 2006 does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '560 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '560 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also

does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Nozaki further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Nozaki does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(14) Omacor PDR

The Omacor PDR is the Physicians' Desk Reference describing Omacor.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '560 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Omacor PDR further do not disclose or suggest a method administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the

recited fatty acid compositions, dosage, or administration period. The Omacor PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to Claim 11, the Omacor PDR does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction based on a comparison to a placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effects. With respect to Claims 5 and 15, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claims 6 and 16, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '560 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. The cited portions of Satoh further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. Satoh further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Satoh does not disclose or suggest a method to effect a reduction in TG in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(16) Shinozaki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '560 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. The cited portions of Shinozaki

further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited dosage or administration period. Shinozaki further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Shinozaki does not disclose or suggest a method to effect a reduction in TG in the subject with the claimed TG levels based on a comparison to placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '560 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration

of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1 and 11 of the '560 Patent (and therefore all asserted claims), Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Takaku further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect to effect the recited TG reduction in the subject with the claimed TG level. With respect to Claim 11, Takaku does not disclose or suggest the recited effect based on a comparison to a placebo control.

Further, with respect to Claims 2 and 12, this reference fails to disclose or suggest the subject having the recited baseline LDL-C levels. With respect to Claims 3 and 13, this reference fails to disclose or suggest the subject having the recited baseline lipid levels. With respect to Claims 4, 7, 14 and 17, this reference fails to disclose or suggest the recited TG and LDL-C effects in the subject with the claimed TG level. With respect to Claims 5 and 15, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the subject with the claimed TG level. With respect to Claims 6 and 16, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8-10 and 18-20, this reference fails to disclose or suggest the recited capsule dosage.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '560 patent would have been *prima facie* obvious in light of the references cited, either

alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '560 patent. Specifically, Defendants do not contend that the relied upon references disclose the following element of Claim 11 (and therefore its dependent claims as well): administering the claimed pharmaceutical composition to the recited subject to effect a reduction in triglycerides based on a comparison to placebo control. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '560 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '560 patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claims of the '560 patent Would Have Been Obvious

(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 '560 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 '560 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."[4147] 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.[4148, 4149] 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.[4150] Defendants' unsupported cobbling

[4147] Defendants' Joint Invalidity Contentions at 574.

[4148] 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, Mataki, 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 2000, 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 Invalidity Contentions at 573.

[4149] 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 Invalidity Contentions at 572.

[4150] *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

of selective disclosures represents hindsight reconstruction.[4151] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[4152] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claims of the '560 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO

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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).

[4151] *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").

[4152] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[4153]

The analysis of the independent claims of the '560 patent is incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '560 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to

[4153] *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").

that of the drug. Any observed effect could be placebo dependent.[4154] As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-high or high TG patients, was expected. At the priority date of the '560 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[4155] This is an incorrect characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C.

[4154] *See* Grimsgaard at 652 (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.)

[4155] Defendants' Joint Invalidity Contentions at 575.

Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[4156] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

[4156] Defendants' Joint Invalidity Contentions at 575.

Nishikawa,[4157] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[4158]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[4159] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[4160] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[4161] Katayama does not disclose *any* LDL-C related data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that

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[4157] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI_2 and PGI_3 Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[4158] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[4159] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[4160] Defendants' Joint Invalidity Contentions at 574 and 575.

[4161] Katayama at 2.

reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[4162] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[4163] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[4164] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[4165] However, when analyzing the lipid

[4162] *Id.* at 16.

[4163] Defendants' Joint Invalidity Contentions at 574.

[4164] Matsuzawa at 7 and 19.

[4165] *Id.* at 23.

impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[4166] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[4167] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG

[4166] *Id.* at 10.

[4167] *Id.* at 11.

levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[4168] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[4169] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '560 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '560 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a

[4168] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

[4169] *See, e.g.*, Rambjor.

reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[4170] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28

[4170] Nozaki at 256.

patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[4171] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[4172] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Further, Defendants have failed to offer a purported combination of references as part of their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any motivation to combine Nozaki and Hayashi with the other references of their purported

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[4171] Hayashi at 26, Table I.

[4172] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

obviousness combinations. Therefore, Defendants should be precluded from relying on these references.

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[4173] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

[4173] Defendants' Joint Invalidity Contentions at 577.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[4174] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[4175] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state

[4174] Mori 2006 at 96.

[4175] Leigh-Firbank at 440.

of the art and numerous publications cited by Defendants.[4176] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "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."[4177] Although teaching away is fact-dependent, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[4178]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[4179] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the HDL_2-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[4180] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may

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[4176] *See, e.g.* Grimsgaard at 654.

[4177] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[4178] *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.").

[4179] Mori 2000 at 1092.

[4180] Mori 2000 at 1088.

be favorable."[4181] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[4182] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '560 patent Is Not Obvious Over the Omacor PDR/Lovaza PDR, in combination with Katayama and/or Matsuzawa, and/or Takaku, further in view of Nozaki and/or

[4181] Mori 2000 at 1092.

[4182] *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."[4183] 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.[4184] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[4185] Defendants' contentions are no more than an assertion that certain

[4183] Defendants' Joint Invalidity Contentions at 574.

[4184] *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).

[4185] *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").

claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[4186] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '560 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[4187]

The analysis of the independent claims of the '560 patent is incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to

[4186] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[4187] *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").

Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '560 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.I.3.c.1.a.i.a.i, incorporated herein by reference, Katayama and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[4188] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

[4188] Defendants' Joint Invalidity Contentions at 577.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[4189] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[4190] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in 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."[4191] 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

[4189] Defendants state in their Joint Invalidity 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).

[4190] Grimsgaard at 654.

[4191] Defendants' Joint Invalidity 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)			Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change	F test: P^1	DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58[2]	−0.22 ± 0.31[3]	1.23 ± 0.57	−0.15 ± 0.40[4]	1.22 ± 0.55	0.11 ± 0.34[4]	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[5]	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[3]	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[5]	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[5]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07[3]	0.96 ± 0.13	0.04 ± 0.08[3]	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[4]	4.70 ± 1.24	−0.13 ± 0.47[5]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[4192] 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."[4193] 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

[4192] Grimsgaard at 657.

[4193] Grimsgaard at 654.

it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard 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." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[4194] A person of ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[4195] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[4196] based on long-term administration.[4197]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a

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[4194] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to 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.

[4195] Defendants' Joint Invalidity Contentions at 577.

[4196] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[4197] Takaku at ICOSAPENT_DFNDT00006834.

conclusion "only from the results of the present study."[4198] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[4199]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[4200] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[4201] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[4202] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other

[4198] Takaku at ICOSAPENT_DFNDT00006897.

[4199] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[4200] Takaku at ICOSAPENT_DFNDT00006884.

[4201] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[4202] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

times.[4203] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[4204]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[4205] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[4206] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '560 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted

[4203] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[4204] Takaku at ICOSAPENT_DFNDT00006897.

[4205] Takaku at ICOSAPENT_DFNDT00006897.

[4206] *See, e.g.*, Rambjor.

claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[4207] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person

[4207] Nozaki at 256.