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12

13 **IN THE UNITED STATES DISTRICT COURT**
14 **FOR THE DISTRICT OF NEVADA**

15 AMARIN PHARMA, INC. *et al.*,

16 Plaintiffs,

17 v.

18 WEST-WARD PHARMACEUTICALS CORP.,
19 *et al*

20 Defendants.

Case No.: 2:16-cv-02525-MMD-NJK

(Consolidated with 2:16-cv-02562-MMD-NJK
and 2:16-cv-02658-MMD-NJK)

PLAINTIFFS' PRELIMINARY VALIDITY
CONTENTIONS PURSUANT TO
LPR 1-10

CONFIDENTIAL

TABLE OF CONTENTS

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

- I. INTRODUCTION 10
- II. PERSON OF ORDINARY SKILL IN THE ART AND INVENTION DATE 16
 - A. Person of Ordinary Skill in the Art 16
 - B. Priority Date of the Asserted Claims 16
- III. STATE OF THE ART 17
 - A. Introduction..... 17
 - B. Key Concepts in Lipid Science..... 20
 - 1. Lipids 21
 - 2. Lipoproteins 22
 - 3. Dyslipidemia 27
 - C. In Treating Hypertriglyceridemia, the Very High TG Group Was Considered Substantially Different than Other Groups 32
 - 1. ATP-III and Practicing Physicians Recognized Different Primary Risks and Treatment Goals for Very-high TG Patients 33
 - 2. It Was Well Understood that Very-high TG Patients Reacted to TG-Lowering Medications Differently than Other TG Groups..... 35
 - 3. The FDA Followed the ATP-III Classifications in Reviewing TG Lowering Drugs 35
 - 4. Very-High TG Patients Often Presented with Visible Symptoms..... 36
 - D. Drugs Approved to Treat High TG Patients Prior to VASCEPA 36
 - 1. Niacin..... 36
 - 2. Fibrates and Prescription Omega-3s 37
 - E. A Person of Ordinary Skill Did Not Differentiate Between EPA and DHA’s TG-Lowering Mechanism or LDL-C impact 43
 - 1. A Person of Ordinary Skill Understood EPA and DHA had the Same TG-Lowering Mechanism..... 44

1	2.	A Person of Ordinary Skill in the Art Did Not Differentiate Between EPA and DHA When Discussing the LDL-C Impact of Prescription Omega-3 Fatty Acids in Patients with Very-High TG Levels.....	47
2			
3			
4	F.	Studies Were Inconclusive Regarding Differential Effects of EPA and DHA.....	49
5	IV.	DESCRIPTION OF REFERENCES	51
6	A.	General Overview	51
7	1.	Defendants Fail to Provide Studies Directed to the Very-High TG Patient Population	51
8	2.	Studies That Were Not Placebo Controlled.....	54
9	3.	Japanese Studies.....	55
10	4.	Studies That Administered EPA and DHA in Varying Concentrations	55
11	5.	Studies which administered only EPA or only DHA.....	57
12	B.	Summary of Prior Art References.....	57
13	1.	WO '118.....	57
14	2.	WO '900.....	58
15	3.	Agren.....	60
16	4.	Ando.....	61
17	5.	Calabresi	62
18	6.	Chan 2002 II	64
19	7.	Chan 2003	65
20	8.	Childs	67
21	9.	Conquer 1996.....	68
22	10.	Contacos.....	69
23	11.	Geppert.....	70
24	12.	Grimsgaard.....	71

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

13.	Hamazaki	72
14.	Hayashi	73
15.	Katayama	75
16.	Kelley	76
17.	Kris-Etherton.....	79
18.	Kurabayashi	79
19.	Leigh-Firbank	80
20.	Lovaza PDR.....	82
21.	Lovegrove	83
22.	Maki	84
23.	Mataki	85
24.	Matsuzawa	86
25.	Mori 2000.....	89
26.	Mori 2006.....	90
27.	Nakamura.....	93
28.	Nelson	94
29.	Nestel	95
30.	Nozaki	96
31.	Okumura	97
32.	Omacor PDR.....	98
33.	Park	99
34.	Rambjor.....	101
35.	Saito	102
36.	Sanders.....	105
37.	Satoh	105

1	38.	Shinozaki.....	106
2	39.	Takaku.....	107
3	40.	Theobald	110
4	41.	Virani	111
5	42.	Wojenski	112
6	43.	Woodman.....	112
7	44.	Yokoyama 2007	113
8	45.	Zalewski.....	115
9	V.	Responses to Defendants’ Joint Invalidity Contentions	115
10	A.	The ‘728 Patent.....	117
11	1.	The ‘728 Patent Claims Eligible Subject Matter Under § 101	117
12	2.	The Asserted Claims of the ‘728 Patent Are Not Anticipated by WO ‘118.....	121
13	3.	The Claims of the ‘728 Patent Would Not Have Been Obvious In Light of the Asserted References.....	138
14	4.	The ‘728 Patent is Not Invalid Under § 112.....	293
15	B.	The ‘715 Patent.....	303
16	1.	The ‘715 Patent Claims Eligible Subject Matter Under § 101	303
17	2.	The Asserted Claims of the ‘715 Patent Are Not Anticipated by WO ‘118.....	307
18	3.	The Claims of the ‘715 Patent Would Not Have Been Obvious In Light of the Asserted References.....	324
19	4.	The ‘715 Patent is Not Invalid Under § 112.....	466
20	C.	The ‘335 Patent.....	477
21	1.	The ‘335 Patent Claims Eligible Subject Matter Under § 101	477
22	2.	The Asserted Claims of the ‘335 Patent Are Not Anticipated by WO ‘118.....	481
23			
24			

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

- 3. The Claims of the ‘335 Patent Would Not Have Been Obvious In Light of the Asserted References 498
- 4. The ‘335 Patent is Not Invalid Under § 112 643
- D. The ‘399 Patent 652
 - 1. The ‘399 Patent Claims Eligible Subject Matter Under § 101 652
 - 2. The Asserted Claims of the ‘399 Patent Are Not Anticipated by WO ‘118..... 656
 - 3. The Claims of the ‘399 Patent Would Not Have Been Obvious In Light of the Asserted References 672
 - 4. The ‘399 Patent is Not Invalid Under § 112 810
- E. The ‘677 Patent 820
 - 1. The ‘677 Patent Claims Eligible Subject Matter Under § 101 820
 - 2. The Asserted Claims of the ‘677 Patent Are Not Anticipated by WO ‘118..... 824
 - 3. The Claims of the ‘677 Patent Would Not Have Been Obvious In Light of the Asserted References 839
 - 4. The ‘677 Patent is Not Invalid Under § 112 972
- F. The ‘446 Patent 980
 - 1. The ‘446 Patent Claims Eligible Subject Matter Under § 101 980
 - 2. The Asserted Claims of the ‘446 Patent Are Not Anticipated by WO ‘118..... 984
 - 3. The Claims of the ‘446 Patent Would Not Have Been Obvious In Light of the Asserted References 999
 - 4. The ‘446 Patent is Not Invalid Under § 112 1130
- G. The ‘652 Patent 1139
 - 1. The ‘652 Patent Claims Eligible Subject Matter Under § 101 1139
 - 2. The Asserted Claims of the ‘652 Patent Are Not Anticipated by WO ‘118..... 1143

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

- 3. The Claims of the ‘652 Patent Would Not Have Been Obvious In Light of the Asserted References 1158
- 4. The ‘652 Patent is Not Invalid Under § 112 1293
- H. The ‘920 Patent 1302
 - 1. The ‘920 Patent Claims Eligible Subject Matter Under § 101 1302
 - 2. The Asserted Claims of the ‘920 Patent Are Not Anticipated by WO ‘118..... 1306
 - 3. The Claims of the ‘920 Patent Would Not Have Been Obvious In Light of the Asserted References 1321
 - 4. The ‘920 Patent is Not Invalid Under § 112 1444
- I. The ‘560 Patent 1452
 - 1. The ‘560 Patent Claims Eligible Subject Matter Under § 101 1452
 - 2. The Asserted Claims of the ‘560 Patent Are Not Anticipated by WO ‘118..... 1456
 - 3. The Claims of the ‘560 Patent Would Not Have Been Obvious In Light of the Asserted References 1472
 - 4. The ‘560 Patent is Not Invalid Under § 112 1603
- J. The ‘650 Patent 1612
 - 1. The ‘650 Patent Claims Eligible Subject Matter Under § 101 1612
 - 2. The Asserted Claims of the ‘650 Patent Are Not Anticipated by WO ‘118..... 1616
 - 3. The Claims of the ‘650 Patent Would Not Have Been Obvious In Light of the Asserted References 1631
 - 4. The ‘650 Patent is Not Invalid Under § 112 1760
- K. The ‘929 Patent 1769
 - 1. The ‘929 Patent Claims Eligible Subject Matter Under § 101 1769
 - 2. The Asserted Claims of the ‘929 Patent Are Not Anticipated by WO ‘118..... 1773

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

3.	The Claims of the '929 Patent Would Not Have Been Obvious In Light of the Asserted References.....	1788
4.	The '929 Patent is Not Invalid Under § 112.....	1921
L.	The '698 Patent.....	1929
1.	The '698 Patent Claims Eligible Subject Matter Under § 101	1929
2.	The Asserted Claims of the '698 Patent Are Not Anticipated by WO '118.....	1933
3.	The Claims of the '698 Patent Would Not Have Been Obvious In Light of the Asserted References.....	1948
4.	The '698 Patent is Not Invalid Under § 112.....	2069
M.	The '372 Patent.....	2078
1.	The '372 Patent Claims Eligible Subject Matter Under § 101	2078
2.	The Asserted Claims of the '372 Patent Are Not Anticipated by WO '118.....	2082
3.	The Claims of the '372 Patent Would Not Have Been Obvious In Light of the Asserted References.....	2097
4.	The '372 Patent is Not Invalid Under § 112.....	2228
N.	The '594 Patent.....	2237
1.	The '594 Patent Claims Eligible Subject Matter Under § 101	2237
2.	The Asserted Claims of the '594 Patent Are Not Anticipated by WO '118.....	2241
3.	The Claims of the '594 Patent Would Not Have Been Obvious In Light of the Asserted References.....	2256
4.	The '594 Patent is Not Invalid Under § 112.....	2387
5.	The '594 Patent is Not Invalid for Obviousness-Type Double Patenting	2395
O.	Objective Indicia of Non-Obviousness.....	2397
1.	Unexpected Results.....	2397
2.	Long-Felt Need and Failure of Others	2424

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24

3. Skepticism..... 2434
4. Industry Praise 2436
5. Copying..... 2439
6. Commercial Success 2439

1 **I. INTRODUCTION**

2 On June 9, 2017, Defendants Dr. Reddy’s Laboratories, Inc., Dr. Reddy’s Laboratories,
3 Ltd., Teva Pharmaceuticals USA, Inc., Andrx Labs, LLC, West-Ward Pharmaceutical Corp., and
4 West-Ward Pharmaceuticals International Ltd. (collectively, “Defendants”) served Plaintiffs
5 Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Ltd. (collectively, “Amarin” or
6 “Plaintiffs”) with Joint Preliminary Invalidity Contentions (“Defendants’ Joint Invalidity
7 Contentions”) for the asserted claims of U.S. Patent Nos. 8,293,728 (“the ’728 patent”),
8 8,318,715 (“the ’715 patent”), 8,357,677 (“the ’677 patent”), 8,367,652 (“the ’652 patent”),
9 8,377,920 (“the ’920 patent”), 8,399,446 (“the ’446 patent”), 8,415,335 (“the ’335 patent”),
10 8,426,399 (“the ’399 patent”), 8,431,560 (“the ’560 patent”), 8,440,650 (“the ’650 patent”),
11 8,518,929 (“the ’929 patent”), 8,524,698 (“the ’698 patent”), 8,546,372 (“the ’372 patent”), and
12 8,617,594 (“the ’594 patent”) (collectively, the “asserted patents” or the “patents-in-suit”).¹
13 Pursuant to Local Patent Rule 1-10, Plaintiffs hereby provide to Defendants the following
14 Responses to Defendants’ Joint Invalidity Contentions.

15 The Asserted Claims of the ’728 patent are Claims 1-19; the Asserted Claims of the ’715
16 patent are Claims 1-19; the Asserted Claims of the ’677 patent are Claims 1-9; the Asserted
17 Claims of the ’652 patent are Claims 1-18; the Asserted Claims of the ’920 patent are Claims 1-
18 10; the Asserted Claims of the ’446 patent are Claims 1-11; the Asserted Claims of the ’335
19 patent are Claims 1-29; the Asserted Claims of the ’399 patent are Claims 1-9; the Asserted
20 Claims of the ’560 patent are Claims 1-20; the Asserted Claims of the ’650 patent are Claims 1-
21 14; the Asserted Claims of the ’929 patent are Claims 1-9; the Asserted Claims of the ’698 patent

22
23 _____
24 ¹ The asserted claims of the Patents-in-Suit were identified in Plaintiffs’ Preliminary Infringement Contentions,
served by Amarin on April 7, 2017.

1 are Claims 1-8; the Asserted Claims of the '372 patent are Claims 1-25; and the Asserted Claims
2 of the '594 patent are Claims 1-7 and 10-26.

3 Plaintiffs reserve the right to amend or supplement these contentions as discovery
4 proceeds in this case, as the Court construes the claims, and as permitted by the Court and the
5 Nevada Local Patent Rules. In particular, fact discovery has just begun, no depositions have
6 taken place, nor has any expert discovery commenced. Further, claim construction proceedings
7 have not yet begun and the Court has not construed the claims of the Asserted Patents.²

8 Plaintiffs also reserve their right to amend or supplement these contentions in the event that
9 Defendants amend their contentions to set forth additional combinations of references that it
10 alleges render obvious any of the asserted claims, or in the event that any Defendant later
11 produces references and/or amends its contentions to provide more specific information
12 regarding any references. Furthermore, with respect to objective indicia of non-obviousness,
13 Plaintiffs reserve the right to amend or supplement these contentions as discovery proceeds in
14 this case. Plaintiffs further reserve their rights to amend or modify these contentions in the event
15 that the Court adopts particular claim constructions.

16 Defendants' Invalidity Contentions do not comply with Nevada Local Patent Rule (Local
17 Pat. R.) 1-8, which requires Defendants to (1) indicate whether "each item of prior art"
18 anticipates or renders obvious each asserted claim, and if obviousness is alleged, (2) explain why
19 the alleged prior art renders the asserted claims obvious, and (3) identify "any combinations of
20 prior art showing obviousness." Defendants have submitted over 650 alleged prior art references
21 in their contentions and failed to (1) indicate whether each item of alleged prior art anticipates or
22

23 ² Accordingly, these contentions should not be interpreted as a statement of Plaintiff's position with respect to the
24 construction of any claim terms.

1 renders obvious each asserted claim, (2) explain why the alleged prior art renders the asserted
2 claims obvious, and (3) identify “any combinations of prior art showing obviousness.”

3 In Exhibit O to Defendants’ Joint Invalidity Contentions, Defendants improperly list over
4 650 alleged prior art references. Defendants provide no specificity and do not even indicate
5 whether a particular reference is relied upon for anticipation or obviousness. Defendants do not
6 formulate a specific theory of alleged *prima facie* obviousness of any claim of the asserted
7 patents and fail to articulate their alleged invalidity challenge with the required specificity. For
8 example, the Defendants do not: (1) identify which of these 650 references, or which portion of
9 the reference, is being relied upon; (2) indicate whether any of the 650 references are relied upon
10 alone or in some identified combination; or (3) identify which specific claims are allegedly
11 obvious over a specific reference or combination. Instead of crystallizing one or more theories
12 of either anticipation or obviousness as the Local Rules require, Defendants broadly reserve the
13 right to rely on any of the over 650 references and provide the specificity and detail required by
14 the Local Rules at some future date. Such wholesale importation of prior art does not comply
15 with the specific requirements of Local Pat. R. 1-8. Defendants’ generalized, purportedly non-
16 limiting contentions do not comply with the Local Rules and do not allow Plaintiffs an
17 opportunity to fairly respond to Exhibit O given the absence of any explanation defining how
18 each alleged prior art reference is being relied upon for anticipation or obviousness.

19 Defendants’ Joint Invalidity Contentions are separately inadequate and do not comply
20 with Nevada’s Local Patent Rules because they do not formulate a specific theory of alleged
21 *prima facie* obviousness of any claim of the asserted patents and fail to focus their alleged
22 invalidity challenge. For example, on pgs. 13-23 of Defendants’ Joint Invalidity Contentions,
23 Defendants list 77 alleged prior art references from the 650 alleged prior art references listed in
24

1 Exhibit O. Although Defendants provide summaries of these 77 alleged prior art references in
2 pgs. 26-155 of their Contentions, Defendants again fail to: (1) provide any indication of whether
3 a reference is being relied upon for anticipation or obviousness; (2) explain how each alleged
4 prior art reference relied upon for obviousness renders the asserted claims obvious; or (3)
5 identify the specific combinations of alleged prior art relied on to allegedly establish obviousness
6 of any specific claim.

7 For example, with respect to anticipation, Defendants specifically identify only one
8 alleged prior art reference, WO 2007/142118, as anticipatory. Although Local Pat. R. 1-8(c)
9 makes clear that a simple declaration that alleged prior art renders asserted claims obvious is
10 insufficient, Defendants rely on exactly such an assertion—that each of the 77 alleged prior art
11 references either anticipates or renders obvious each asserted claim. Nevada’s Local Patent
12 Rules require Defendants set forth an explanation or theory of why the alleged prior art renders
13 the asserted claims obvious, and identify “any combinations of prior art showing obviousness.”
14 Defendants’ attempt to rely on any or all of the 77 alleged prior art references, without providing
15 anything more than generalized and conclusory statements, deprives Plaintiffs of the “parity,”
16 “focus,” and notice contemplated by the Local Patent Rules.

17 Similarly, Defendants’ disclosure with respect to the prior art products Epadel and
18 Lovaza/Omacor is inadequate and does not comply with Nevada’s Local Patent Rules.
19 Defendants make the unsupported assertion that these products “anticipate and/or render obvious
20 on or more of the Asserted Claims, alone or in combination with the prior art listed above.”³
21 Defendants, however offer no explanation as to how or why these products would render the
22 asserted claims anticipated or obvious, nor do they identify “any combinations of prior art
23

24 ³ Defendants’ Joint Invalidity Contentions at 24.

1 showing obviousness.” Accordingly, Defendants have not properly disclosed any invalidity
2 contention with respect to these products. Plaintiffs reserve the right to move to strike any
3 attempt by Defendants to belatedly offer invalidity arguments relying on these products.

4 Defendants also characterize their Joint Contentions as “non-limiting, illustrative,”⁴ and
5 apparently reserve the right to add additional references, combinations and theories. Plaintiffs
6 clearly cannot respond to unstated invalidity theories or compilations of broad assertions without
7 any grounding in specific asserted claims or combinations of alleged prior art references.⁵

8 For all the reasons stated above, Plaintiffs reserve the right to oppose Defendants’
9 attempts to amend their contentions, under Local Patent Rule 1-12, to add additional invalidity
10 theories, prior art, prior art combinations, or other disclosures not fairly presented in Defendants’
11 Joint Invalidation Contentions, served on June 10, 2017. Plaintiffs also reserve the right to strike
12 any subsequent submissions, briefing or attempts to belatedly disclose new invalidity positions,
13 including but not limited to expert reports or testimonies articulating a theory or prior art
14 combination not fairly presented in Defendants’ Joint Invalidation Contentions. Plaintiffs object to
15 Defendants’ attempt to improperly incorporate by reference wholesale a number of different
16 documents, including “all documents and prior art references cited in any one or more of the
17 Patents-in-Suit, as well as any related patents and applications, including their respective
18 prosecution histories, including those filed in the United States or in a foreign country and those
19 listed for the reference listed drug in FDA’s Orange Book.”⁶ This is not an adequate disclosure.

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22 ⁴ See, e.g., Defendants’ Joint Invalidation Contentions at 205-206.

23 ⁵ For example, Defendants’ Joint Invalidation Contentions at pgs. 205 and 213 baldly state “It would have been
24 obvious to replace the active ingredient in Lovaza with pure EPA” and “It would have been obvious to administer
purified EPA in the dosing regimen recited in the claims of the ’728 Patent.”

⁶ Defendants’ Joint Invalidation Contentions at 9.

1 Defendants further improperly reserve their right to supplement their contentions “at any
2 time and for any reason” and for a number of other improper reasons. Such a reservation has no
3 effect and is inconsistent with the Local Patent Rules. Plaintiffs reserve the right to oppose any
4 such attempt by Defendants to supplement their contentions.

5 In their contentions, Defendants appear to suggest that there was inequitable conduct,⁷
6 but no Defendant actually pled inequitable conduct in their respective Answers to Amarin’s
7 Complaint. Therefore, their assertion of inequitable conduct is not a proper part of this case.
8 Nor do Defendants’ conclusory statements in the Contentions come close to meeting the standard
9 for an allegation of inequitable conduct. Plaintiffs dispute Defendants’ claim that the Amarin
10 March 2010 Next Generation Lipid Modifications in Cardiovascular Disease presentation
11 contained statements “in direct conflict with representations that were made with an intent to
12 deceive the Patent Office during the prosecution of the Patents-in-Suit.”⁸ Defendants citation to
13 a post-invention presentation provides no evidence of inequitable conduct. Defendants appear to
14 conflate Amarin’s views regarding the patented subject matter in 2010 with the view of a number
15 of declarants regarding what a person of skill in the art would have believed *prior to the*
16 *invention*. That is not the correct inquiry. Plaintiffs have complied with the duty of candor and
17 good faith in the prosecution of the asserted patents, including compliance with their duty to
18 disclose to the USPTO all information known by Plaintiffs to be material to patentability.⁹
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22 ⁷ Defendants’ Joint Invalidity Contentions at 24.

23 ⁸ *Id.*

24 ⁹ *See* 37 C.F.R. § 1.56.

1 **II. PERSON OF ORDINARY SKILL IN THE ART AND INVENTION DATE**

2 **A. Person of Ordinary Skill in the Art**

3 The person of ordinary skill in the art to whom the Patents-in-Suit are directed has an
4 advanced degree (such as a Ph.D., M.D., or D.O.) and advanced training and expertise in lipid
5 metabolism or cardiology, or has experience in the diagnosis, evaluation, and treatment of lipid
6 blood disorders.¹⁰

7 “A person of ordinary skill in the art is . . . presumed to be one who thinks along the line
8 of conventional wisdom in the art and is not one who undertakes to innovate . . . [through]
9 expensive, systematic research or by extraordinary insights.”¹¹ For this reason, the inventors of
10 the Patents-in-Suit are not considered persons of ordinary skill in the art—they “possess
11 something . . . which sets them apart from the workers of *ordinary* skill, and one should not go
12 about determining obviousness under § 103 by inquiring into what *patentees* (i.e., inventors)
13 would have known or would likely have done.”¹²

14 **B. Priority Date of the Asserted Claims**

15 The asserted claims are entitled to a priority date of no later than March 2008.¹³ Any
16 references cited by Defendants dated March 2008, or later, are therefore not prior art to the
17 asserted claims.

18 As explained in Plaintiffs’ Infringement Contentions submitted pursuant to LPR 1-6,
19 even if the asserted claims are not entitled to the March 2008 priority date, the asserted claims
20

21 ¹⁰ See *Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust*, 956 F. Supp. 2d 429 (S.D.N.Y.
2013) *aff’d*, 764 F.3d 1366 (Fed. Cir. 2014).

22 ¹¹ *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985); see also *KSR Int’l Co. v. Teleflex Inc.*,
550 U.S. 398, 421 (2007) (“A person of ordinary skill is also a person of ordinary creativity.”).

23 ¹² *Standard Oil*, 774 F.2d at 454.

24 ¹³ See, e.g., AMRN01672057–58, AMRN01688238, AMRN01688512.

1 are entitled to the priority date of at least U.S. Provisional Patent Application No. 61/151,291,
2 filed on Feb. 10, 2009, and U.S. Provisional Patent Application No. 61/173,755, filed on Apr. 29,
3 2009.

4 **III. STATE OF THE ART**

5 **A. Introduction**

6 The Patents-in-Suit relate to a drug named VASCEPA, which is designed to treat “severe
7 (≥ 500 mg/dL) hypertriglyceridemia,” a kind of lipid disorder in the blood. Lipids are fats found
8 in the body, some of which circulate in the blood, including triglycerides (“TGs”) and
9 cholesterol. Because TGs and cholesterol are hydrophobic molecules, they move through the
10 bloodstream in particles called “lipoproteins,” which consist of a lipid core (TGs and cholesterol
11 esters) coated with a layer of additional lipids (phospholipids and sphingomyelin), with various
12 apolipoproteins attached, which determine lipoprotein function. There are five main types of
13 lipoproteins, which are classified based, in part, on their TG to cholesterol ratio.

Lipoprotein ¹⁴	Triglycerides	Cholesterol
Chylomicrons	85-90%	2-7%
VLDL (very low density lipoproteins)	55-80%	5-15%
IDL (intermediate density lipoproteins)	20-50%	20-40%
LDL (low density lipoproteins)	5-15%	40-50%
HDL (high density lipoproteins)	5-10%	15-25%

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23 ¹⁴ Bays, et al., *Prescription Omega-3 Fatty Acids and Their Lipid Effects: Physiologic Mechanisms of Action and Clinical Implications*, 6 EXPERT REV. CARDIOVAS. THER. 391, 395 (2008) (“Bays 2008 I”).

24 CONFIDENTIAL

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2 Because chylomicrons and VLDL particles carry the most TGs, they are referred to as
3 “triglyceride-rich” lipoproteins.¹⁵ As the TG-rich lipoproteins travel through the bloodstream,
4 the TGs are hydrolyzed and cleared from the lipoprotein.¹⁶ As the TGs are removed the VLDL
5 particles become smaller, denser, TG depleted and more cholesterol-rich LDL particles.¹⁷ While
6 VLDL, IDL, and LDL particles could be considered to on a continuum of lipoprotein
7 metabolism, HDL particles constitute a functionally distinct class of lipoproteins.

8 Due to a number of genetic or lifestyle factors, TG levels may increase to unhealthy
9 levels in the bloodstream, causing hypertriglyceridemia. Increased TGs may be due to an
10 overproduction of lipoproteins in the liver or intestine, a reduction in the clearance of TGs from
11 lipoproteins, or both.¹⁸ This can lead to an abnormal accumulation of TG-rich lipoprotein
12 particles in the blood, causing overall TG levels to rise, which is referred to as
13 hypertriglyceridemia once TGs reach certain levels.

14 In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on
15 the third report of the National Cholesterol Education Program’s Adult Treatment Panel (the
16 “ATP-III”) for authoritative guidance on the treatment of lipid disorders.¹⁹ The ATP-III divided
17 hypertriglyceridemia patients into three classes based on the levels of TG in their blood—

18
19 ¹⁵ *Id.* at 393.

20 ¹⁶ Peter O. Kwiterovich, *Lipid, Apolipoprotein, and Lipoprotein Metabolism: Implications for the Diagnosis and Treatment of Dyslipidemia*, in *The Johns Hopkins Textbook of Dyslipidemia* 1, 4-5 (Peter O. Kwiterovich Jr. ed., 2009) (“Kwiterovich in Kwiterovich”).

21 ¹⁷ *Id.*

22 ¹⁸ *National Institutes of Health, National Heart, Lung, and Blood Institute, “Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report*, 106 *CIRCULATION* 3143, 3331 (2002) (“ATP-III”).

23 ¹⁹ *Id.*

1 | borderline-high (150-199 mg/dL), high (200-499 mg/dL), and very-high TGs (≥ 500 mg/dL)—
2 | and recommended substantially different treatment strategies for patients depending on
3 | classification.²⁰

4 | For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to
5 | reduce risk of coronary heart disease.²¹ Accordingly, in these populations, physicians focused on
6 | lowering cholesterol carried in LDL particles (or “LDL-C”).²² In this patient population,
7 | lowering of TG levels and the levels of cholesterol carried on all atherogenic lipoproteins
8 | (termed non-HDL-C), were considered secondary treatment goals. In contrast, the primary goal
9 | for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life
10 | threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In
11 | very high TG patients, lowering LDL-C is a secondary treatment goal.²³

12 | The ATP-III recommended a combination of lifestyle changes and TG lowering
13 | medication for very high TG patients.²⁴ Prior to the priority date of the asserted patents, several
14 | drugs were approved to treat very-high TGs, including niacin, fibrates, and a prescription omega-
15 | 3 fatty acids called “Lovaza” (formerly known as “Omacor”).²⁵ However, in working with these
16 | drugs (except niacin), physicians faced the significant challenge of increased LDL-C.²⁶

19 | ²⁰ *Id.* at 3335.

20 | ²¹ *Id.*

21 | ²² *Id.*

22 | ²³ *Id.*

23 | ²⁴ *Id.*

24 | ²⁵ Because “Omacor” and “Lovaza” both refer to the same drug, the names are used interchangeably herein.

²⁶ See Weintraub May 23, 2011 Decl., ¶ 8; Bays May 23, 2011 Decl., ¶ 8.

1 These increases in LDL-C in patients with very high TG levels were cause for concern, in
2 light of the link between LDL-C and atherosclerosis identified by the ATP-III. For example, the
3 FDA required a warning in the Lovaza labeling instructing physicians to ensure that LDL-C
4 levels did not rise excessively.²⁷

5 The LDL-C rise observed in patients with very high TG levels receiving TG-lowering
6 therapy was also expected because it was understood that fibrates and Lovaza worked, at least in
7 part, by increasing the transformation of VLDL particles into LDL particles.²⁸ Because very-
8 high TG patients generally have a large backlog of VLDL particles in the blood—due to over
9 production of VLDL or a reduced rate of transformation to LDL particles—persons of ordinary
10 skill expected that LDL levels would increase as the conversion of VLDL to LDL progressed
11 with TG lowering.²⁹ This phenomenon was not only expected, but also observed for both
12 fibrates and omega-3 fatty acids.

13 B. **Key Concepts in Lipid Science**

14 To provide context regarding the state of the art, this section provides a brief review of
15 the science associated with lipid blood disorders as it was understood just before the invention
16 date of the Patents-in-Suit.

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19 ²⁷ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza packaging insert).

20 ²⁸ See Harold E. Bays, *Fish Oils in the Treatment of Dyslipidemia and Cardiovascular Disease*, in THE JOHNS
21 HOPKINS TEXTBOOK OF DYSLIPIDEMIA 245, 247 (Peter O. Kwiterovich Jr. ed., 2009) (“Bays in Kwiterovich”);
22 Michael A. Miller, *Disorders of Hypertriglyceridemia*, in THE JOHNS HOPKINS TEXTBOOK OF DYSLIPIDEMIA 74, 86
(Peter O. Kwiterovich Jr. ed., 2009) (“Miller in Kwiterovch”); McKenney & Sica, *Role of Prescription Omega-3*
Fatty Acids in the Treatment of Hypertriglyceridemia, 27 PHARMACOTHERAPY 715, 720 (2007) (noting that fish oil
increases the conversion rate of TG rich particles into LDL) (“McKenney 2007”).

23 ²⁹ See Harold E. Bays, *Rationale for Prescription Omega-3-Acid Ethyl Ester Therapy for Hypertriglyceridemia: A*
24 *Primer for Clinicians*, 44 DRUGS OF TODAY 205, 213 (2008) (“Bays 2008 II”) (“[T]herapies that reduce the number
of [TG rich] particles are sometimes accompanied by an increase in LDL-C levels.”).

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1. Lipids

The term “lipid” refers to a diverse group of molecules that perform a variety of functions in the human body. All lipids are at least partially “hydrophobic”—meaning they cannot mix with water—and some are completely hydrophobic. Some lipids found in the bloodstream include fatty acids, triglycerides, and cholesterol.

a) Fatty Acids and Triglycerides

Fatty acids are the basic form of fat used by the body. While some fatty acids are synthesized in the body, others must be obtained from dietary sources. Fatty acids that are necessary to the body’s health but cannot be produced by the body are referred to as “essential” fatty acids.

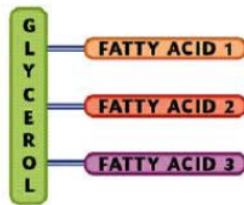
Fatty acids can be saturated or unsaturated. Saturation refers to available space within the carbon chain for hydrogen atoms to bond. A fatty acid is saturated if all available bonds are occupied with hydrogen atoms. Unsaturated fats have double bonds between individual carbon atoms in the chain, reducing the places available for hydrogen bonding. Monounsaturated fats have one double bond, and polyunsaturated fats have two or more double bonds.

Fatty acids can be attached to other elements, including carbohydrates. The most common configuration is a triglyceride—which is three fatty acids attached to glycerol, a particular carbohydrate (*See* Figure 1). Saturated or unsaturated fatty acids may be attached to the glycerol. TGs are the most prevalent source of transported and stored fat in the body. The fatty acids are attached to glycerol by an “ester bond” that is broken by hydrolysis when the TG is degraded.

Figure 1³⁰

³⁰ Katherine L. Soly, MD, FACC, *Cholesterol and Triglyceride: What’s it all about?* MEDIaID (Oct. 11, 2012), <http://www.medibid.com/blog/2012/10/cholesterol-and-triglyceride-whats-it-all-about/>.

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b) Cholesterol

Cholesterol is a type of lipid produced naturally in the body and used for a variety of structural functions. Although the body produces all the cholesterol it needs, cholesterol is also found in some dietary sources. Statins inhibit the biosynthesis of cholesterol. Cholesterol can be in a free form that is partially hydrophobic, or in an ester form that is completely hydrophobic. Cholesterol ester is the primary form of cholesterol transported by lipoproteins.

2. Lipoproteins

Because TGs and cholesterol esters are hydrophobic, they are transported through the blood in “lipoproteins.”³¹ Lipoproteins consist of a lipid core, containing TGs and cholesterol esters, surrounded by a surface coat of additional lipids (phospholipids and sphingomyelin), with various apolipoproteins attached, which determine lipoprotein function.³² The surface lipids protect the lipid core from interacting with the water in human plasma.

As noted above, there are five major categories of lipoproteins, which are classified based on their density. The density of a lipoprotein is determined in part by the ratio of TGs to cholesterol within the lipoprotein. The main lipoprotein categories, with their associated triglyceride and cholesterol content are listed below.

Lipoprotein	Triglycerides	Cholesterol
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³¹ See Bays 2008 I, at 393.
³² See Kwiterovich in Kwiterovich at 2.

Chylomicrons	85-90%	2-7%
VLDL (very low density lipoproteins)	55-80%	5-15%
IDL (intermediate density lipoproteins)	20-50%	20-40%
LDL (low density lipoproteins)	5-15%	40-50%
HDL (high density lipoproteins)	5-10%	15-25% ³³

Each lipoprotein was known to play a different role in the movement of lipids through the body.

a) Chylomicrons and VLDL: TG-rich lipoproteins

Chylomicrons and VLDL particles were known as the “TG-rich” lipoproteins.³⁴ The TGs within chylomicrons and VLDL particles originate from different sources, and they follow different paths within the body.

(1) Chylomicrons

Chylomicrons were understood to contain TGs obtained from dietary fat (referred to as an “exogenous” source).³⁵ The pathway of chylomicrons through the body as it was understood at the time of invention is illustrated in Figure 2, below. Once consumed, TGs are broken down and then repackaged in the intestine, together with cholesterol, protein, and other components, into a chylomicron.³⁶ The chylomicron is released into circulation in the body, where it interacts

³³ *Id.*; Bays 2008 I, at 395.

³⁴ Bays 2008 I, at 393.

³⁵ Kwiterovich *in* Kwiterovich, at 4.

³⁶ *Id.*

1 with enzymes called lipases (e.g. “lipoprotein lipase” or “LPL” in the capillaries).³⁷ Lipases
2 partially “hydrolyze” the TGs in chylomicrons, or break the bond between the fatty acids and the
3 glycerol backbone which forms the TGs.

4 Once the fatty acids are no longer bonded to the glycerol and released as “free fatty
5 acids,” they are released from the lipoprotein.³⁸ Free fatty acids are delivered to tissues
6 throughout the body, where they are further processed to create energy or reassembled into TGs
7 and stored for future use (*i.e.* in adipose tissue; the primary site of fat storage with the body).³⁹

8 TG-depleted chylomicrons are smaller, denser and are referred to as “chylomicron
9 remnants.”⁴⁰ Chylomicron remnants return to the liver for further processing.⁴¹

20 ³⁷ *Id.*

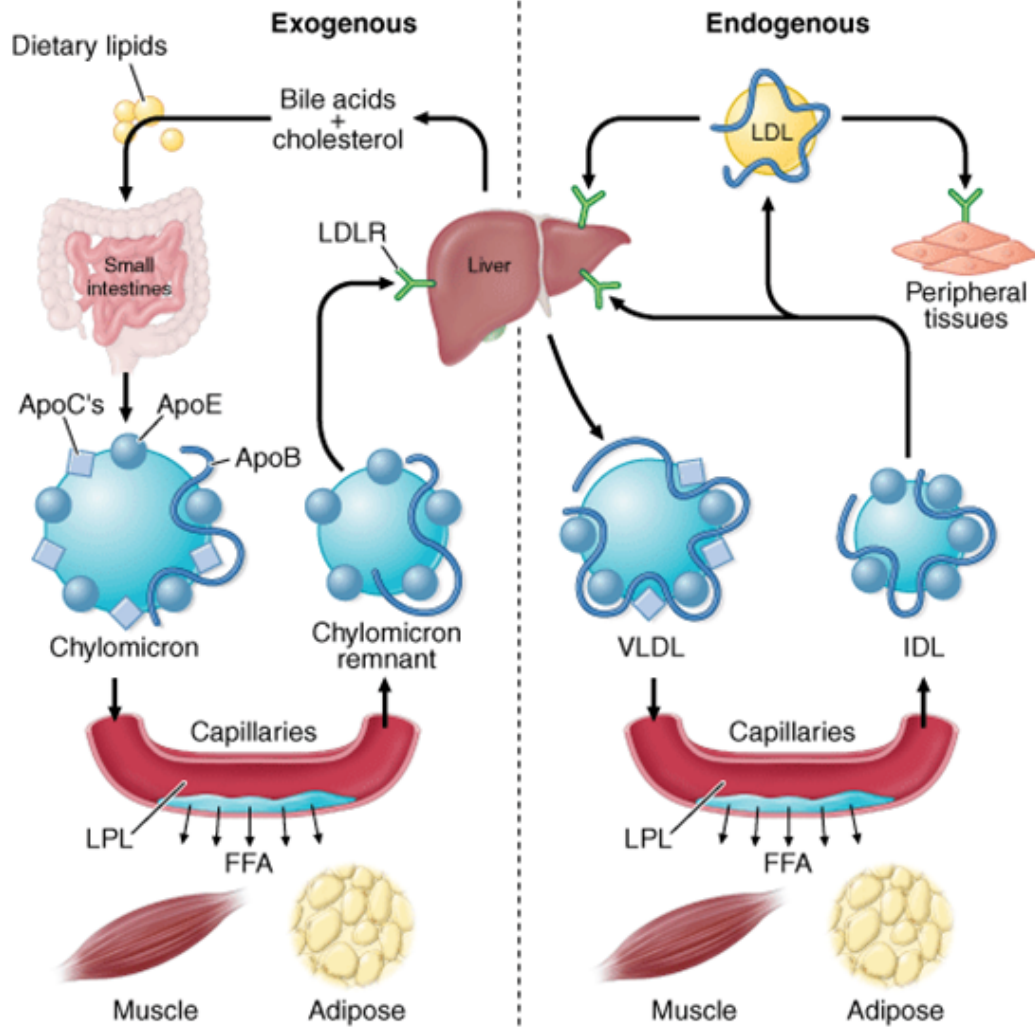
21 ³⁸ *Id.*

22 ³⁹ *Id.*

22 ⁴⁰ *Id.*

23 ⁴¹ Robert W. Mahley & Thomas P. Bersot, *Drug Therapy for Hypercholesterolemia and Dyslipidemia*, in GOODMAN
24 & GILMAN’S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 971, 974 (Joel G. Hardman *et al* eds., 10th ed. 2001)
 (“Goodman & Gilman”).

Figure 2⁴²



⁴² Anthony Fauci et al., *Disorders of Lipoprotein Metabolism*, Harrison's Internal Medicine 2418 (17 ed. 2008) (Figure 350-2) (available at <http://dualibra.com/wp-content/uploads/2012/04/037800~1/Part%2015.%20Endocrinology%20and%20Metabolism/Section%203.%20Disorders%20of%20Intermediary%20Metabolism/350.htm>).

1 (2) VLDL, IDL, and LDL

2 VLDL particles were generally known to comprise around 90% of the total TG-carrying
3 lipoproteins in the blood.⁴³ TGs in VLDL particles are synthesized by the liver (or
4 “endogenously”) from free fatty acids, cholesterol, proteins and other components circulating in
5 the bloodstream or produced in the liver.⁴⁴

6 Figure 2 above shows the path of VLDL particles through the body as it was understood
7 at the time of invention. VLDL particles are secreted by the liver into the bloodstream. As with
8 chylomicrons, lipases hydrolyze the bond between the fatty acids and glycerol in the TGs in the
9 VLDL particles, releasing free fatty acids into circulation, where they can be further processed
10 for energy by tissues throughout the body or repacked into TGs within storage tissues (*i.e.*
11 adipose tissue).⁴⁵ The smaller, denser, more cholesterol-rich remnants of the VLDL particles
12 remain in the bloodstream until they are taken up by the liver or other tissues.⁴⁶ Based on their
13 new composition, these remnants are referred to as IDL.⁴⁷ About half the IDLs are cleared from
14 the blood by the liver, while the other half undergoes further hydrolysis that further depletes the
15 remaining TGs.⁴⁸ Once an IDL particle contains 10% or less TGs, and all of its surface proteins
16 except Apolipoprotein B (or “Apo-B”) are removed, it is transformed into a LDL particle.⁴⁹

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18 ⁴³ Bays 2008 I, at 392.

19 ⁴⁴ Kwiterovich *in* Kwiterovich, at 4; Rafael A. Cox & Mario R. Garcia-Palmieri, *Cholesterol, Triglycerides, and*
20 *Associated Lipoproteins*, in CLINICAL METHODS: THE HISTORY, PHYSICAL, AND LABORATORY EXAMINATIONS 153
(H. Kenneth Walker, W. Dallas Hall, J. Willis Hurst eds., 3rd ed. 1990) (*available at*
<http://www.ncbi.nlm.nih.gov/books/NBK351>) (“Cox”).

21 ⁴⁵ Bays 2008 I, at 393.

22 ⁴⁶ Kwiterovich *in* Kwiterovich, at 5.

23 ⁴⁷ *Id.*

24 ⁴⁸ Goodman & Gilman at 975.

⁴⁹ *Id.*

1 LDL particles generally account for about two thirds of a patient’s total blood
2 cholesterol.⁵⁰ Nearly half of all LDL particles are cleared from the bloodstream by the liver,
3 while the rest (along with the cholesterol they carry: LDL-C⁵¹) are distributed throughout
4 peripheral tissues and arteries, including coronary arteries.⁵²

5 (3) HDL: The “good” cholesterol

6 As of the invention date, HDL was known to do essentially the opposite of LDL—rather
7 than depositing cholesterol in peripheral tissues, it removes cholesterol from tissue and transports
8 it back to the liver for removal.⁵³ Because it was understood that HDL performs this function,
9 high levels of HDL-C in the blood were understood to correlate with reduced atherosclerotic
10 risk.⁵⁴

11 **3. Dyslipidemia**

12 Dyslipidemia is an umbrella term encompassing various disorders associated with
13 elevated lipid levels in a person’s blood. At the time of invention, patients with dyslipidemia
14 were known to be at risk of cardiovascular disease, pancreatitis, and other serious conditions.
15 The Patents-in-Suit claim a method of treatment for a particular kind of dyslipidemia—severe
16 hypertriglyceridemia (≥ 500 mg/dL).

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20 ⁵⁰ *Id.* at 976; ATP-III at 3163.

21 ⁵¹ When a “-C” is added to the lipoprotein abbreviations, reference is being made to the cholesterol carried by that lipoprotein.

22 ⁵² James M. McKenney, *Dyslipidemias, Atherosclerosis, and Coronary Heart Disease*, in *Applied Therapeutics: The Clinical Use of Drugs* 13-1, 13-2 and 13-4 (Wayne A. Kradjan ed., 8th ed. 2005) (“McKenney 2005”).

23 ⁵³ *Id.* at 13-4.

24 ⁵⁴ *Id.*; ATP-III at 3163.

1 a) Hypertriglyceridemia

2 Hypertriglyceridemia occurs when the level of TGs in a person's bloodstream exceeds
3 150 mg/dL. In the 2000s, physicians looked to the ATP-III to provide strategy for managing
4 patients with hypertriglyceridemia. The ATP-III divided hypertriglyceridemia into three
5 categories based on overall plasma TG levels.

6

7 Classification ⁵⁵	Serum Triglyceride Levels
8 Normal triglycerides	Less than 150 mg/dL
9 Borderline-high triglycerides	150-199 mg/dL
10 High triglycerides	200-499 mg/dL
11 Very-high triglycerides	≥ 500 mg/dL

12 b) Causation

13 As of the invention date, persons of ordinary skill in the art understood that a variety of
14 causes could lead to abnormally elevated TG levels, including genetic and lifestyle factors. The
15 presence of these factors were known to lead to, among other things, overproduction of TG-rich
16 VLDL particles and/or decreased transformation of VLDL to LDL, both of which could cause
17 TG levels in the bloodstream to rise.⁵⁶ Demographic factors were also understood to influence a
18 person's baseline lipid profile.

19 (1) Genetic Disorders

20 Persons of ordinary skill were familiar with a number of genetic conditions that could
21 cause elevated TGs. Some of these conditions increased the production of either chylomicrons

22 _____
23 ⁵⁵ ATP-III at 3331.

24 ⁵⁶ *Id.* at 3332 (“Many persons with very-high triglycerides have both overproduction and defective catabolism”).

1 or VLDL, while others decreased LPL activity, leading to reduced clearance of TG-rich
2 lipoproteins.⁵⁷ While genetic disorders leading to hypertriglyceridemia were comparatively rare,
3 it was understood at the time that the higher a person's baseline TG levels were, the more likely
4 genetic factors were at play.⁵⁸

5 (2) Diet and Exercise

6 Persons of ordinary skill in the art also understood that both diet and exercise level could
7 have significant impacts on TG levels. Heavy consumption of carbohydrates, certain kinds of
8 fats, and/or alcohol was understood to lead to increased TG levels.⁵⁹ And more generally,
9 obesity was known to correlate with both overproduction of VLDL particles and decreased
10 transformation of VLDL to LDL.⁶⁰

11 In contrast, it was understood that regular exercise could offset the TG effects of some
12 dietary factors and decrease TG levels.⁶¹ Accordingly, lack of regular exercise and/or sedentary
13 lifestyle were known to correlate with higher TG levels.⁶²

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⁵⁷ Kwiterovich *in* Kwiterovich, at 9-17.

20 ⁵⁸ McKenney 2007 at 716 (The higher the [TG] level, the more likely genetics play a role.”).

21 ⁵⁹ Miller *in* Kwiterovich, at 85; Daniel J. Rader, *Lipid Disorders*, *in* TEXTBOOK OF CARDIOVASCULAR MEDICINE 55,
59 (Eric J. Topol ed., 3rd ed. 2007) (“Rader *in* Topol”).

22 ⁶⁰ McKenney 2005 at 13-6.

23 ⁶¹ Miller *in* Kwiterovich, at 85; ATP-III at 3179.

24 ⁶² ATP-III at 3179.

1 (3) Age and Gender

2 Age and gender were also known to have significant effects on baseline TG levels.

3 Between birth and middle-age TG and cholesterol levels can increase 4-5 fold.⁶³ Further, in
4 some countries, both TGs and cholesterol rise steadily between 20 and 50-60 years of age.⁶⁴

5 Gender was also known to play a role in lipid levels. While men and women usually
6 have similar levels of TGs and cholesterol from birth to 50 years of age, women tend to have
7 higher values than men beyond age 50.⁶⁵ Women generally have higher HDL and lower VLDL
8 particle levels than men.⁶⁶

9 c) Risks of Hypertriglyceridemia: Atherosclerosis and Pancreatitis

10 Patients with hypertriglyceridemia were understood to be at risk of experiencing
11 cardiovascular events, pancreatitis, or both, based on which ATP-III category they fell into.

12 (1) Atherosclerosis

13 Patients with borderline-high or high TG levels were understood to be at risk of
14 “atherosclerosis,” or the build-up of cholesterol in arteries, which can lead to heart disease if it
15 occurs in the cardiovascular system.⁶⁷ While LDL, IDL, and VLDL particles all had the
16 potential to contribute to atherosclerosis, persons of ordinary skill in the art believed as of the
17 invention date that LDL was the most “abundant and clearly evident atherogenic lipoprotein.”⁶⁸

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20 ⁶³ *Classification of Hyperlipidaemias and Hyperlipoproteinaemias*, 43 BULLETIN OF THE WORLD HEALTH ORGANIZATION 891, 896 (1970) (“WHO”).

21 ⁶⁴ *Id.*

22 ⁶⁵ *Id.*

23 ⁶⁶ *Id.*; see also Kwiterovich in Kwiterovich at 8.

24 ⁶⁷ See Rader in Topol, at 55; ATP-III at 3163.

⁶⁸ ATP-III at 3163.

1 Thus LDL-C was thought to make “the greatest contribution to the development of
2 atherosclerotic risk.”⁶⁹

3 In addition to LDL-C levels, physicians also relied on two other important markers in to
4 gauge atherosclerotic risk: Apolipoprotein B and non-HDL-C. Apolipoproteins make up part of
5 the phospholipid coating that covers the lipid core of lipoproteins. Apolipoprotein B (or “Apo-
6 B”) was known to be present in the coatings of all atherogenic lipoprotein particles—VLDL,
7 IDL, and LDL.⁷⁰ Because it was a direct measurement of atherogenic lipoprotein particles, Apo-
8 B was known to “have a strong predictive power for severity of coronary atherosclerosis and
9 [coronary heart disease] events.”⁷¹ Thus, while LDL-C levels were the benchmark for
10 atherosclerotic risk, physicians also considered Apo-B to be an important indicator.⁷²

11 Non-HDL-C is the measure of total atherogenic cholesterol in the body, which is
12 calculated by subtracting HDL-C (the “good” cholesterol) from total cholesterol levels.⁷³
13 Because both non-HDL-C and Apo-B are essentially measuring the same value—presence of
14 atherogenic lipoproteins in the blood stream—non-HDL-C was understood to be correlated with
15 total Apo-B and to “represent[] an acceptable surrogate marker for total [Apo-B] in routine
16 clinical practice.”⁷⁴

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20 ⁶⁹ McKenney 2005 at 13-2.

21 ⁷⁰ ATP-III at 3170; Bays 2008 I, at 395.

22 ⁷¹ ATP-III at 3170.

23 ⁷² *Id.*

24 ⁷³ *Id.* at 3169.

⁷⁴ *Id.* at 3170.

1 (2) Pancreatitis

2 In addition to atherosclerosis, patients with very-high TG levels were known to be at risk
3 of pancreatitis, a condition with significant potential morbidity.⁷⁵ The risk of acute pancreatitis
4 was understood to increase in proportion to the rise in TG levels. Chylomicrons are generally
5 formed within 1-5 hours after a meal and cleared within 12 hours.⁷⁶ However, when TG levels
6 exceed 500 mg/dL, chylomicrons continue to be present in fasting plasma.⁷⁷ It was known that
7 chylomicrons and their remnants may obstruct pancreatic capillary blood flow, causing the
8 necrosis, edema and inflammation characteristic of pancreatitis.⁷⁸

9 C. **In Treating Hypertriglyceridemia, the Very High TG Group Was
10 Considered Substantially Different than Other Groups**

11 Throughout the 2000s, treatment strategies for patients with hypertriglyceridemia differed
12 substantially based on where the patient fell within the ATP-III TG level classifications.⁷⁹ This
13 was especially the case with respect to the very-high TG group (≥ 500 mg/dL), which was known
14 to have different primary risks and therefore require different treatment methods, than the
15 borderline-high (150-199 mg/dL) and high (200-499 mg/dL) TG groups.⁸⁰ Further, it was
16 widely understood that patients in the very-high TG group would often react differently to drugs
17 used to treat the borderline-high or very-high TG group.⁸¹ Recognizing these crucial differences
18

19 ⁷⁵ *Id.* at 3335; Rader *in* Topol, at 67; Bays *in* Kwiterovich, at 248-249.

20 ⁷⁶ Cox at 154.

21 ⁷⁷ *See* ATP-III at 3332.

22 ⁷⁸ Bays *in* Kwiterovich, at 248.

23 ⁷⁹ ATP-III at 3335.

24 ⁸⁰ *See id.*

⁸¹ *See* Bays 2008 II at 214-15 (noting that the same drug caused LDL-C to go down in borderline-high TG patients and go up in very-high TG patients).

1 between the ATP-III populations, the FDA approved some drugs specifically for the very-high
2 TG group without granting treatment indications for the borderline-high or high TG
3 populations.⁸²

4 Based on these distinctions, a person of ordinary skill in the art, prior to the invention of
5 VASCEPA, would have viewed individuals with very-high TGs as a “unique patient population”
6 that “substantially and clinically” differed from patients in other TG classifications.⁸³ The key
7 differences between populations are discussed in further detail below.

8 **1. ATP-III and Practicing Physicians Recognized Different Primary**
9 **Risks and Treatment Goals for Very-high TG Patients**

10 a) **Borderline-high and High TG Patients: Reducing Atherosclerotic**
11 **Risk**

11 As noted above, the ATP-III identified atherosclerosis as the primary risk faced by
12 borderline-high and high TG patients (150-499 mg/dL).⁸⁴ Because LDL particles were
13 considered at the time to be the “most abundant” atherogenic lipoprotein,⁸⁵ lowering LDL-C was
14 the chief treatment concern for both borderline-high and high TG populations.⁸⁶ In high TG
15 patients, non-HDL-C was a secondary target that could be lowered by either LDL-C-lowering or
16 TG-lowering therapies.⁸⁷

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20 ⁸² See Bays Jan. 8, 2012 Decl., ¶ 22.

21 ⁸³ *Id.*, ¶ 23.

22 ⁸⁴ ATP-III at 3335.

23 ⁸⁵ *Id.* at 3163.

24 ⁸⁶ *Id.* at 3335.

⁸⁷ *Id.*

1 To treat borderline-high and high patients, the ATP-III recommended a combination of
2 lifestyle changes (i.e. diet and exercise) and an LDL-C lowering drug therapy.⁸⁸ For the latter,
3 physicians often relied on a class of drugs called statins, which were known to be effective at
4 reducing LDL-C.⁸⁹ If statin therapy were optimized, additional TG-lowering therapy was
5 recommended to further reduce non-HDL-C.

6 b) Very High TG Patients: Risk of Pancreatitis

7 In contrast, for the very-high TG population a person of ordinary skill in the art would
8 have understood that the primary risk faced by very-high TG patients (≥ 500 mg/dL) was acute
9 pancreatitis, a potentially life threatening condition.⁹⁰ While atherosclerosis remained a concern
10 for these patients, the threat of pancreatitis was viewed as more serious, and the ATP-III and
11 persons of ordinary skill in the art therefore prioritized TG reduction over lowering LDL-C or
12 increasing HDL-C.⁹¹

13 As with the borderline-high and high patients, treating very-high TG patients involved
14 both lifestyle changes and medication.⁹²

19 _____
20 ⁸⁸ *Id.* at 3334-35.

21 ⁸⁹ *Id.*

22 ⁹⁰ *Id.* at 3335; Rader *in Topol*, at 67.

23 ⁹¹ See ATP-III at 3356; Weintraub May 23, 2011 Decl., ¶ 7 (“In patients with very-high [TGs], the initial aim of
24 therapy is to prevent acute pancreatitis through [TG] lowering.”); Bays 2008 I at 391 (“For patients with very-high
TG levels . . . the initial therapeutic goal is to lower TG levels to prevent pancreatitis.”).

⁹² Bays May 16, 2011 Decl., ¶ 7.

1 **2. It Was Well Understood that Very-high TG Patients Reacted to TG-**
2 **Lowering Medications Differently than Other TG Groups**

3 Prior to the invention of VASCEPA, it was widely understood that patients reacted
4 differently to TG-lowering medications depending on their baseline TG levels.⁹³ Accordingly,
5 because very-high TG groups started with severely elevated baseline TG levels (≥500 mg/dL),
6 their responses to drug treatment were often vastly different from the responses of the other TG
7 groups (150-499 mg/dL). Therefore, one could not simply assume that a lipid lowering agent
8 would have the same effects in a patient with borderline-high to high TG levels, as a patient with
9 very-high TG levels. For example, some fibrates, a class of drugs commonly used to treat lipid
10 disorders prior to the invention of VASCEPA (and discussed in more detail below), were known
11 to have opposite effects on normal/borderline-high and very-high TG patients—while they may
12 have *lowered* both TGs and LDL-C in normal to borderline-high TG patients, they *increased*
13 LDL-C in very-high TG patients.⁹⁴

14 **3. The FDA Followed the ATP-III Classifications in Reviewing TG**
15 **Lowering Drugs**

16 Recognizing the important differences between very-high TG patients and the lower TG
17 classifications, the FDA incorporated the ATP-III distinctions into its regulatory review process,
18 granting pharmaceutical treatment indications for the very-high TG populations for some drugs
19 while not doing so for the borderline-high or high TG groups.⁹⁵ For example, Lovaza/Omacor,

20 ⁹³ Weintraub Sept. 7, 2011 Decl., ¶ 8 (“[P]atients with borderline-high/high [TGs] . . . can respond very differently
21 to [TG] lowering therapy than do subjects with very-high [TGs].”); Bays Jan. 8, 2012 Decl., ¶ 26 (referring to “the
22 well-accepted scientific dogma that patients having the worst baseline metabolic abnormalities (whether it be high
23 triglyceride levels, high glucose levels, etc.) often have the highest degree of responses to metabolic drug therapies,
24 when compared to patients who do not have the greatest degree of metabolic abnormalities”).

⁹⁴ 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).

⁹⁵ Bays Jan. 8, 2012 Decl., ¶ 22.

1 discussed in detail below, was (and is) approved to treat very-high TG patients, but not high or
2 borderline-high TG patients.⁹⁶

3 **4. Very-High TG Patients Often Presented with Visible Symptoms**

4 Patients with very-high TG levels were also known to present physical symptoms that
5 were not seen in patients with borderline-high or high triglycerides. For example, patients with
6 certain genetic disorders leading to very high TG levels sometimes exhibited eruptive xanthoma,
7 a dermatological condition characterized by small red bumps.⁹⁷ Others presented with lipemia
8 retinalis, a white discoloration of the retina.⁹⁸

9 In light of these key differences associated with the very-high TG population, a person of
10 ordinary skill did not rely on, nor expect to be able to predict, the effect of a treatment strategy
11 on very-high TG patients based on studies relating to borderline-high or high TG patients.

12 **D. Drugs Approved to Treat High TG Patients Prior to VASCEPA**

13 Before the priority date of the patents-in-suit, several drugs were approved to help lower
14 TG levels for treatment of the very-high TG group, including niacin, fibrates, and prescription
15 omega-3 medication.⁹⁹ As discussed in more detail below, each of these drugs presented a major
16 challenge in the treatment of very-high TG patients.

17 **1. Niacin**

18 Niacin is one of the drugs approved to treat very-high TG patients.¹⁰⁰ While they were
19 known to be effective at simultaneously reducing TGs and LDL-C, niacin was associated with

20 ⁹⁶ *Id.*

21 ⁹⁷ See ATP-III at 3333; see also Kwiterovich in Kwiterovich at 14.

22 ⁹⁸ Kwiterovich in Kwiterovich at 14.

23 ⁹⁹ Rader in Topol at 61.

24 ¹⁰⁰ Goodman & Gilman at 991.

1 highly undesirable side effects—including “flushing” (or reddening of the face and other areas
2 with a burning sensation) and dyspepsia—that limited patients’ willingness to take them.¹⁰¹
3 Attempts to modify niacin to eliminate side effects were unsuccessful.¹⁰² As a result of these
4 side effects, niacin were underutilized in treating very-high TG patients.¹⁰³ Niacin was
5 understood to have a different mechanism of action than omega-3s and fibrates.

6 2. Fibrates and Prescription Omega-3s

7 Fibrates and prescription omega-3 medications were also approved for the treatment of
8 very-high TG (≥ 500 mg/dL) patients prior to the invention of VASCEPA. While the
9 mechanisms by which both achieved TG lowering were not perfectly understood, it was well
10 accepted that they operated at least in part by improving the rate of conversion of VLDL
11 particles to LDL particles.¹⁰⁴ Because most very-high TG patients start with an immense build-
12 up of TG-rich VLDL particles (either due to overproduction of VLDL or defective VLDL
13 clearance), persons of ordinary skill in the art naturally expected LDL levels (and consequently
14 LDL-C) to increase in patients taking these drugs as the conversion of VLDL to LDL particles
15 increased.¹⁰⁵

17 ¹⁰¹ 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).

18 ¹⁰² Weintraub Sept. 7, 2011 Decl., ¶ 21.

19 ¹⁰³ *Id.*

20 ¹⁰⁴ Bays *in* Kwiterovich, at 247; Kwiterovich *in* Kwiterovch, at 86; Bays 2008 I, at 398 (noting that EPA and DHA
can “enhance[] TG clearance from circulating [TG rich] particles”); McKenney 2007 at 720 (noting that fish oil
increases the conversion rate of TG rich particles into LDL).

21 ¹⁰⁵ See Bays May 16, 2011 Decl., ¶ 8; Weintraub Sept. 7, 2011 Decl., ¶ 14 (noting that labeling for approved fibrates
warned that LDL levels could increase significantly); Bays 2008 II, at 213 (“[T]herapies that reduce the number of
22 [TG rich] particles are sometimes accompanied by an increase in LDL-C levels.”); Goodman & Gilman at 993
23 (noting that “LDL levels rise in many patients, especially hypertriglyceridemic patients” treated with a particular
kind of fibrate); Bays 2008 I, at 401-402; Harris et al., *Safety and Efficacy of Omacor in Severe*
24 *Hypertriglyceridemia*, 4 J. OF CARDIOVASCULAR RISK 385, 388 (1997) (“Harris 1997”); McKenney 2007 at 720.

1 a) Fibrates

2 Prior to the invention of VASCEPA, several fibrates were approved to treat very-high TG
3 patients, including Lopid, Tricor, and Trilipix.¹⁰⁶

4 Fibrates were known to have different lipid effects on patients depending on where they
5 fell in the ATP-III classifications. In normal (≤ 150 mg/dL) and borderline-high TG patients
6 (150-199 mg/dL), fibrates were known to significantly lower LDL-C levels.¹⁰⁷ However, in high
7 TG patients (200-499 mg/dL), some fibrates mildly increased LDL-C. For example, in patients
8 with normal baseline TG values receiving Tricor, LDL-C decreased by about 31%.¹⁰⁸ In patients
9 with a mean baseline TG value of 231.9 mg/dL, LDL-C again decreased significantly (about
10 20%).¹⁰⁹ However, for patients with a mean baseline TG value of 432 mg/dL, there was a non-
11 significant increase in LDL-C.¹¹⁰ Similar results were seen with the administration of Lopid
12 (gemfibrozil tablets) as well.¹¹¹

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17 ¹⁰⁶ Weintraub Sept. 7, 2011 Decl., ¶ 14.

18 ¹⁰⁷ Bays in Kwiterovich, at 247.

19 ¹⁰⁸ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

20 ¹⁰⁹ *Id.*

21 ¹¹⁰ *Id.* See also, Trilipix, Full Prescribing Information 1, 27 (Revised Dec. 2008) ("Trilipix Label").

22 ¹¹¹ See Otvos *et al.*, *Low-Density Lipoprotein and High-Density Lipoprotein Particle Subclasses Predict Coronary*
23 *Events and Are Favorably Changed by Gemfibrozil Therapy in the Veterans Affairs High-Density Lipoprotein*
24 *Intervention Trial*, 113 CIRCULATION 1556, 1558 (2006) (showing administration of Gemfibrozil to patients with
borderline-high baseline TG levels had no impact on LDL-C levels); Manttari *et al.*, *Effect of Gemfibrozil on the*
Concentration and Composition of Serum Lipoproteins, 81 ATHEROSCLEROSIS 11, 14 and 16 (1990) (stating that the
effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects
with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant
decreases in LDL-C).

1 In contrast, in very-high TG patients (≥ 500 mg/dL), fibrates were known to increase
 2 LDL-C levels, sometimes dramatically.¹¹² For example, Tricor caused a significant increase in
 3 LDL-C by about 45% in patients with very-high triglycerides (mean baseline TG = 726
 4 mg/dL).¹¹³

5 Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
6 Tricor (fenofibrate) ¹¹⁴	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*

8 * = p < 0.05 vs. Placebo

9 A person of ordinary skill in the art at the time would have been troubled by this
 10 phenomenon, in light of the ATP-III's identification of LDL-C goals, but also would have
 11 expected it to occur. Because it was understood that fibrates lowered TG levels, at least in part,
 12 by increasing the conversion of VLDL particles to LDL particles, persons of ordinary skill
 13 viewed the LDL-C rise simply as a consequence of reducing very high TGs.¹¹⁵

14 To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an
 15 LDL-C lowering medication such as a statin.¹¹⁶ This two-drug approach brought its own set of
 16 complications, however. Fibrates were known to be associated with a condition called
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19 ¹¹² Weintraub Sept. 7, 2011 Decl., ¶ 14 (noting that Lopid, Tricor, and Trilipix packaging all warned that LDL could increase significantly).

20 ¹¹³ *Id.* See also, Trilipix Label at 27

21 ¹¹⁴ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

22 ¹¹⁵ See Goodman & Gilman at 993 (noting that fibrates, through various mechanisms, enhance the clearance of VLDL); Bays *in* Kwiterovich, at 247-248.

23 ¹¹⁶ Bays May 16, 2011 Decl., ¶ 8; Rader *in* 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");

1 rhabdomyolysis, or muscle breakdown that could lead to kidney failure.¹¹⁷ Although the
2 percentage of patients in which this condition occurred was relatively small, it increased five-
3 fold, if fibrates were administered with a statin.¹¹⁸ This risk was well documented, and warnings
4 to this effect were included in fibrate labeling.¹¹⁹ As a result, physicians were reluctant to
5 recommend, and patients were hesitant embrace, a combination fibrate/statin course of
6 treatment.¹²⁰ As a result of this and other side effects, fibrates were “relegated to second line
7 status for treating patients with very-high [TGs].”¹²¹

8 b) Prescription Omega-3s

9 (1) Composition

10 Omega-3 fatty acids are a polyunsaturated fatty acid containing three double bonds at
11 specific positions within the hydrocarbon chain.¹²² Omega-3 fatty acids include EPA
12 (eicosapentaenoic acid) and DHA (docosahexaenoic acid),¹²³ which are both found at relatively
13 high levels in certain fatty fish and other seafood.¹²⁴

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16 ¹¹⁷ Weintraub Sept. 7, 2011 Decl., ¶ 15. *See also* Rader *in* Topol at 61 (“[T]here is an increased risk of myopathy associated with the combination of fibrate and statin.”).

17 ¹¹⁸ *See Id.*; McKenney 2007 at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

18 ¹¹⁹ *See* Weintraub Sept. 7, 2011 Decl., ¶ 15 (citing Tricor labeling, a fibrate approved for treatment of very-high TGs).

19 ¹²⁰ *Id.* at ¶ 17

20 ¹²¹ *Id.*

21 ¹²² *Id.*

22 ¹²³ For purposes of these contentions only EPA shall mean ethyl all-cis-5,8,11,14,17-icosapentaenoate or an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid, in any form. For purposes of these contentions only DHA shall mean all-cis-docosa-4,7,10,13,16,19-hexa-enoic acid or an ethyl ester of the omega-3 fatty acid docosahexaenoic acid, in any form.

23 ¹²⁴ Bays *in* Kwiterovich, at 246.

1 (2) Lovaza/Omacor

2 Prior to VASCEPA, FDA had approved only one prescription omega-3 fish oil indicated
3 for very-high TG patients, which was made from a combination of approximately 465 mg EPA
4 and 375 mg DHA.¹²⁵ Originally the drug was named “Omacor” (the name currently used in
5 Europe), but because the name was too similar to another drug (Amicar), the name was changed
6 to “Lovaza” in the United States in 2007.¹²⁶

7 Like fibrates, Lovaza was known to cause different lipid effects in patients based on their
8 baseline TG levels. In studies involving the borderline-high TG population (150-199 mg/dL),
9 Lovaza/Omacor significantly reduced TGs and raised HDL-C,¹²⁷ but had no significant effect on
10 other lipid-related variables, including LDL-C and Apo-B.¹²⁸ In contrast, in the very-high TG
11 population (≥ 500 mg/dL), TGs were reduced by nearly 50% while LDL-C increased sharply by
12 nearly 50%.¹²⁹ Because Lovaza increased LDL-C so intensely in the very high TG population,
13 the FDA required the Lovaza labeling to warn physicians that patients “should be monitored to
14 ensure that LDL-C level does not increase excessively.”¹³⁰

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17 ¹²⁵ See Lovaza®, Physicians’ Desk Reference 2699 (62d ed. 2007) (“Lovaza PDR”); Omacor®, Physicians’ Desk
Reference 2735 (60d ed. 2006) (“Omacor PDR”).

18 ¹²⁶ See July 2007 Letter from Reliant Pharmaceuticals to Pharmacy Professionals,
19 <http://www.ncbop.org/PDF/OmacorBecomesLovazaJuly2007.pdf>

20 ¹²⁷ Chan *et al.*, *Regulatory Effects of HMG CoA Reductase Inhibitor and Fish Oils on Apolipoprotein B-100 Kinetics*
in Insulin-Resistant Obese Male Subjects With Dyslipidemia, 51 DIABETES 2377, 2379-81 (2002) (“Chan 2002 I”).

21 ¹²⁸ *Id.* See also, Westphal *et al.*, *Postprandial chylomicrons and VLDLs in severe hypertriglycerolemia are*
lowered more effectively than are chylomicron remnants after treatment with n-3 fatty acids, 71 AM. J. CLIN. NUTR.
914, 918 (2000).

22 ¹²⁹ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10. See
23 also, Lovaza PDR and Omacor PDR.

24 ¹³⁰ See Weintraub Sept. 7, 2011 Decl., ¶ 23.

1 Although a person of ordinary skill in the art would have been aware of these warnings
2 and the ATP-III guidelines identifying LDL-C as the primary treatment target to reduce
3 cardiovascular risk, a person of ordinary skill in the art would have also been aware of several
4 mitigating factors.

5 First, as with fibrates, increased LDL-C was viewed as a natural consequence of lowering
6 TGs in a patient population for which TG reduction was the primary clinical objective. Although
7 the exact mechanism by which omega-3 fatty acids achieved TG reduction was not clear, there
8 was strong support for the theory that it worked, at least in part, by increasing the conversion of
9 TG-rich VLDL particles to LDL particles.¹³¹ Thus, as with fibrates, treating physicians would
10 have considered the rise in LDL-C to be a direct consequence of TG lowering through increased
11 VLDL particle conversion to LDL.¹³²

12
13 Second, persons of ordinary skill in the art would also have been aware that, despite the
14 increase in LDL-C, most clinical trial evidence demonstrated that omega-3 fatty acids decreased
15 overall atherogenic cholesterol levels, as reflected by a reduction in non-HDL-C.¹³³ Because
16 Lovaza lowered overall bad cholesterol (primarily through the reduction of VLDL particles and
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19 ¹³¹ Bays *in* Kwiterovich, at 247; Harris *et al.*, *Omega-3 fatty acids and Coronary Heart Disease Risk: Clinical and*
20 *Mechanical Perspectives*, 197 *ATHEROSCLEROSIS* 12, 17-19 (2008) (“Harris 2008”).

21 ¹³² Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
22 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
23 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
24 treatment.”); Bays *in* Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
decrease in VLDL.”).

¹³³ Bays *in* Kwiterovich, at 248.

1 their remnants), persons of ordinary skill saw Lovaza as having a net positive benefit despite the
2 rise in LDL-C.¹³⁴

3 Finally, Lovaza was seen as having a safer side-effect profile than fibrates.¹³⁵ Whereas
4 fibrates presented the risk of serious side effects like rhabdomyolysis, the most common adverse
5 experience associated with Lovaza was “fishy burps.” Further, in contrast to fibrates, Lovaza
6 was not known to have any clinically significant drug interactions.¹³⁶ As a result, Lovaza could
7 be safely combined with a statin, without the risks associated with fibrate/statin combinations.¹³⁷

8 In light of these factors, persons of ordinary skill were willing to use Lovaza despite the
9 concern they would have felt about the increase in LDL-C, because there was no better
10 alternative treatment available.

11 E. **A Person of Ordinary Skill Did Not Differentiate Between EPA and DHA’s**
12 **TG-Lowering Mechanism or LDL-C impact**

13 A person of ordinary skill in the art, at the time of the invention, did not differentiate
14 between EPA and DHA when discussing omega-3 fatty acid treatment for patients with
15 hypertriglyceridemia.¹³⁸ Instead, a person of ordinary skill in the art understood that *omega-3*
16 *fatty acids* reduced TG levels in humans and that *EPA and DHA* had similar TG-lowering
17 effects.¹³⁹ Further, it was understood that *omega-3 fatty acids* (which refers to EPA and DHA
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¹³⁴ See *id.*

20 ¹³⁵ *Id.* at 254.

21 ¹³⁶ Bays 2008 I at 398; Bays *in* Kwiterovich at 252.

22 ¹³⁷ See Bays 2008 I at 399.

23 ¹³⁸ See, e.g. Dunbar & Rader, *Demystifying Triglycerides: A Practical Approach for the Clinician*, 72 CLEVELAND
CLINIC JOURNAL OF MEDICINE 661 (2005) (“Dunbar”); Bays 2008 I; Harris 2008.

24 ¹³⁹ Bays 2008 I at 397.

1 collectively) reduced triglycerides by 30% to 40% and was a helpful adjunct to medications.¹⁴⁰

2 It was recommended that patients who needed to lower triglycerides take 2 to 4 g/day of *EPA*
3 *and DHA* as capsules.¹⁴¹

4 **1. A Person of Ordinary Skill Understood EPA and DHA had the Same**
5 **TG-Lowering Mechanism**

6 A person of ordinary skill in the art, at the time of the invention, also did not differentiate
7 the mechanisms by which EPA and DHA reduced serum triglycerides. Indeed, a person of
8 ordinary skill in the art would have understood EPA and DHA to reduce serum triglycerides by
9 the same mechanisms.¹⁴² Although those mechanisms were not completely understood, there
10 was “compelling evidence” that both EPA and DHA reduced levels of plasma TG by (1)
11 reducing hepatic VLDL synthesis and secretion and (2) increasing the transformation of VLDL
12 to LDL.¹⁴³ Scientific publications published around the priority date of the patents in suit,
13 including a 2009 textbook reviewing the state of the art of lipid metabolism in dyslipidemias,
14 referred generically to fish oils or omega-3 fatty acids, and did not differentiate between EPA or
15 DHA.¹⁴⁴ By reducing hepatic VLDL synthesis and secretion, EPA and DHA reduced the

16 _____
17 ¹⁴⁰ Dunbar at 674; Bays I at 397.

18 ¹⁴¹ Dunbar at 675, Table 6; Bays 2008 I at 397.

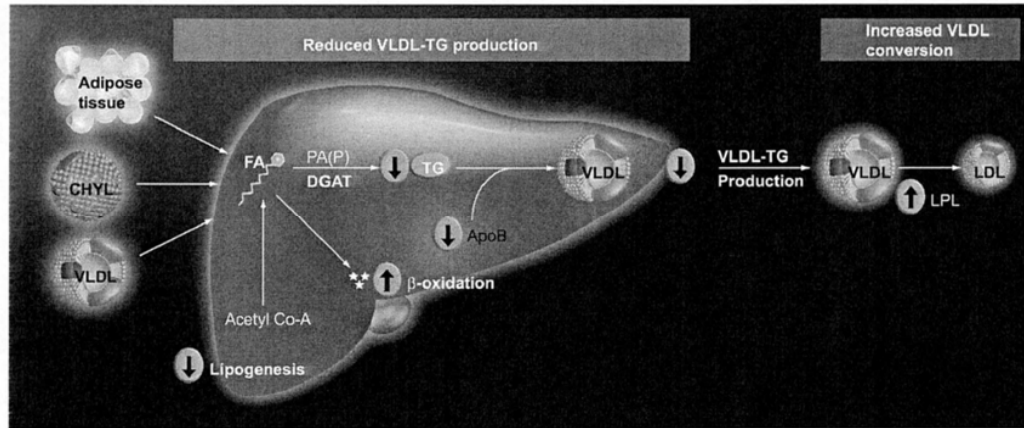
19 ¹⁴² Bays *in* Kwiterovich, at 248, Fig. 21.2.

20 ¹⁴³ Bays 2008 I, at 398; Bays *in* Kwiterovich, at 247.

21 ¹⁴⁴ See, e.g. Dunbar; Bays 2008 I; Harris 2008; The Johns Hopkins Textbook of Dyslipidemia (Peter O. Kwiterovich
22 Jr. Ed., 2009); Eslick et al., *Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-*
23 *analysis*, 136 INT’L J. CARDIOLOGY 4–16 (2009); Clemens von Schacky, *A review of omega-3 ethyl esters for*
24 *cardiovascular prevention and treatment of increased blood triglyceride levels*, 2 Vascular Health and Risk
Management 251 (2006) (“von Schacky 2006”) (“While the results with fish and fish oils have been not as clear cut,
the data generated with the purified ethyl ester forms of these two fatty acids are consistent. Although slight
differences in biological activity exist between EPA and DHA, both exert a number of positive actions against
atherosclerosis and its complications. EPA and DHA as ethyl esters inhibit platelet aggregability, and reduce serum
triglycerides, while leaving other serum lipids essentially unaltered.”) Weber & Raeerstorff, *Triglyceride-lowering*
effect of omega-3 LC-polyunsaturated fatty acids - A review, Nutr Metab Cardiovasc Dis 28 (2000) (“Weber 2000”)

1 number of TG-rich VLDL particles in circulation, thereby decreasing total levels of plasma
2 TG.¹⁴⁵ By enhancing VLDL to LDL conversion, TGs were more effectively cleared from VLDL
3 particles, thereby increasing the conversion of VLDL to IDL and LDL.¹⁴⁶

4 Figure 3.¹⁴⁷



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12 As depicted in Figure 3 above, there were three primary mechanisms by which it was
13 believed that EPA and DHA decreased hepatic VLDL synthesis. First, EPA and DHA were both
14 thought to reduce hepatic VLDL synthesis and production by increasing the rate of hepatic fatty
15 acid oxidation. Increased oxidation of fatty acids decreases the fatty acids available for TG
16 synthesis and the TGs available for incorporation into VLDL particles.¹⁴⁸ Second, both EPA and
17 DHA were thought to reduce hepatic VLDL synthesis and secretion by decreasing the formation

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19 (“Omega-3 LC-PUFA can be seen as agent, that significantly lower triglycerides without greatly affecting total
cholesterol and LDL-C, particularly not in the long-term.”).

20 ¹⁴⁵ Harris 2008 at 16; Bays in Kwiterovich, at 247.

21 ¹⁴⁶ Bays in Kwiterovich, at 247; Harris 2008 at 17-19.

22 ¹⁴⁷ See Bays 2008 I at 396; Bays in Kwiterovich, at 248.

23 ¹⁴⁸ Bays 2008 I 398; Harris & Bulchandani, *Why Do Omega-3 Fatty Acids Lower Serum Triglycerides?*, 17 CURR.
OPIN. LIPIDOL. 387, 390 (2006) (“Harris 2006”) (A review of studies using rats showed that EPA and DHA, in
24 combination, increased fatty acid β -oxidation 14 out of 21 times; EPA increased fatty acid β -oxidation 11 out of 15
times; and DHA increased fatty acid β -oxidation 8 out 11 times.)

1 of fatty acid and TG synthesis in the liver (hepatic lipogenesis).¹⁴⁹ Lastly, both EPA and DHA
2 were thought to reduce hepatic VLDL synthesis and secretion by decreasing activity of
3 triglyceride-synthesizing enzymes such as phosphatidic acid phosphohydrolase (“PAP”) or
4 diacylglycerol acyltransferase (“DGAT”).¹⁵⁰ PAP is an enzyme that catalyzes the conversion of
5 phosphatidic acid to diacylglycerol. DGAT is an enzyme that catalyzes the final step in TG
6 synthesis. By inhibiting PAP and DGAT, omega-3 fatty acids, generically, decrease TG
7 synthesis, reducing VLDL production and decreasing the levels of plasma TG.

8 A person of ordinary skill in the art also understood that omega-3 fatty acids, generically,
9 improved the transformation of VLDL to LDL by increasing LPL activity, thereby aiding TG
10 removal from VLDL (and chylomicron particles).¹⁵¹ In fact, it was known that omega-3 fatty
11 acids, when given individually (4g/day), both significantly increased the rate of chylomicron
12 clearance.¹⁵² Specifically, prescription omega-3 fatty acid therapy, such as Lovaza/Omacor, was
13 thought to increase the conversion of VLDL to IDL and LDL.¹⁵³ A person of ordinary skill
14 understood that the increased conversion of VLDL to LDL was the reason for the increased
15 LDL-C levels in patients with very-high TGs levels when administered EPA and DHA.¹⁵⁴ It was
16 also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty
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19 ¹⁴⁹ Bays 2008 I, 398 (A review of studies using rats showed that EPA and DHA in combination reduced lipogenesis
20 8 out of 8 times; EPA reduced lipogenesis 3 out of 4 times; and DHA reduced lipogenesis 2 out of 2 times.)

21 ¹⁵⁰ Bays 2008 I, 399; Bays III at 247.

22 ¹⁵¹ Bays 2008 I at 399; Bays III at 247.

23 ¹⁵² Harris 2008 at 17-18.

24 ¹⁵³ Bays 2008 I at 397 (*See Fig. 3*); Chan 2002 I at 2381-83; Harris 2008 17-19.

¹⁵⁴ Bays 2008 I at 402.

1 acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the
2 most in patients with the highest baseline TG levels.¹⁵⁵

3 **2. A Person of Ordinary Skill in the Art Did Not Differentiate Between**
4 **EPA and DHA When Discussing the LDL-C Impact of Prescription**
5 **Omega-3 Fatty Acids in Patients with Very-High TG Levels**

6 A person of ordinary skill in the art at the time of the invention did not differentiate
7 between EPA and DHA with respect to the increase in LDL-C that was associated with
8 prescription omega-3 fatty acids (Lovaza/Omacor) in the treatment of severe
9 hypertriglyceridemia. As with fibrates, experts believed that Lovaza/Omacor lowered TG while
10 “commonly” increasing LDL-C in severe hypertriglyceridemic patients.¹⁵⁶ A person of ordinary
11 skill would not attribute the rise in LDL-C to either EPA or DHA—instead it was tied to the TG-
12 lowering mechanism of omega-3 fatty acids, generally, and to the very-high baseline TG levels
13 of severely hypertriglyceridemic patients. It was understood that the degree of LDL-C increase
14 was generally related to the pretreatment TG levels.¹⁵⁷ Because very-high TG patients generally
15 had a large backlog of VLDL particles in the blood—due to over production or reduced
16 transformation of VLDL to LDL—persons of ordinary skill expected that LDL levels would
17 increase as the conversion of VLDL particles into LDL improved.¹⁵⁸

18 Figure 3¹⁵⁹

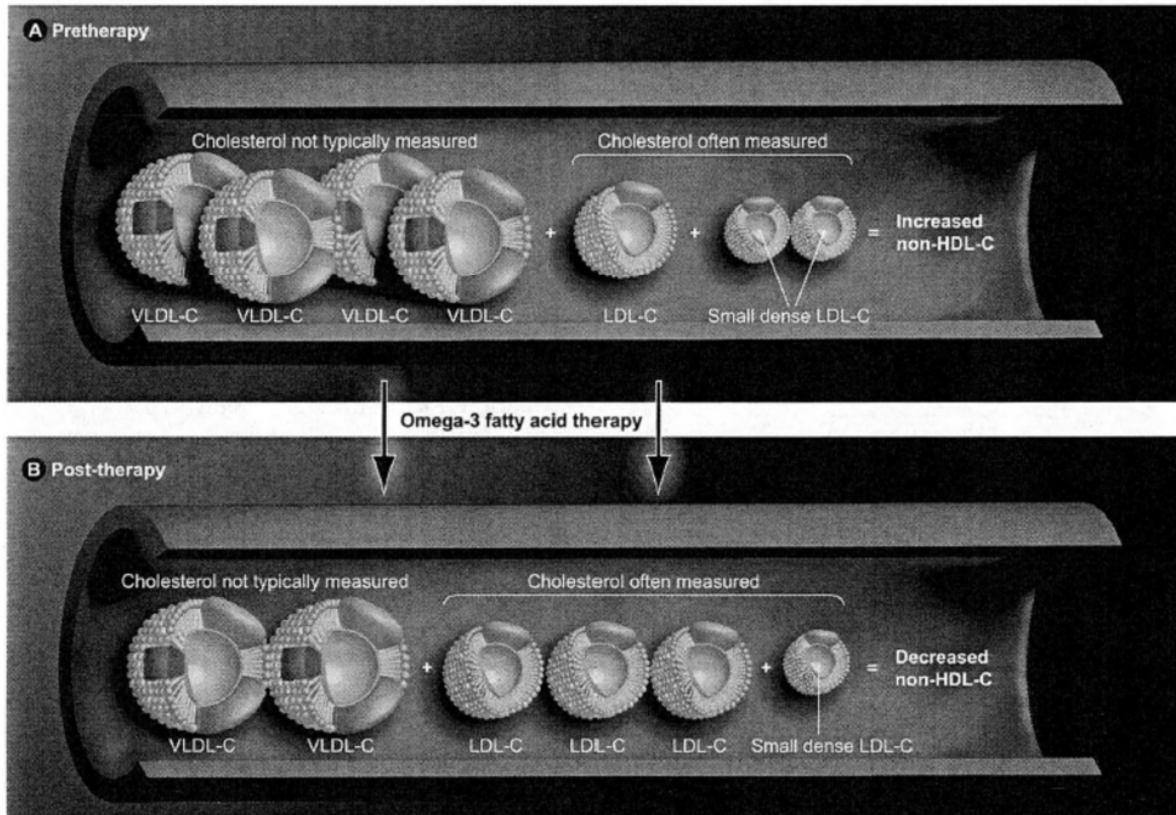
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21 ¹⁵⁵ Bays 2008 I at 400-402.

22 ¹⁵⁶ Bays *in* Kwiterovich, at 248.

23 ¹⁵⁷ Bays 2008 I at 402.

24 ¹⁵⁸ See Bays 2008 II, at 213 (“[T]herapies that reduce the number of [TG rich] particles are sometimes accompanied by an increase in LDL-C levels.”).

¹⁵⁹ Bays 2008 I at 400; Bays *in* Kwiterovich, at 249.



Moreover, the increase in LDL-C caused by omega-3 fatty acids, such as Lovaza/Omacor, was tolerated because the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels. Studies noted that even with increases in LDL-C, omega-3 fatty acids decreased non-HDL-C levels.¹⁶⁰ Experts believed that omega-3 fatty acids' favorable effects on cardiovascular health could be explained by decreased non-HDL-C levels, which was thought may be a better predictor of cardiovascular disease risk than LDL-C alone.¹⁶¹ Furthermore, with omega-3 fatty acid therapy, there was some suggestion that the total number of LDL particles remained relatively constant with a decrease in the small LDL

¹⁶⁰ Bays *in* Kwiterovich, at 248.

¹⁶¹ *Id.*

1 particles and an increase in large LDL particles.¹⁶² Experts understood that an increase in LDL
2 particle size may represent a shift to less atherogenic particles.¹⁶³

3 **F. Studies Were Inconclusive Regarding Differential Effects of EPA and DHA**

4 As of the priority date, there were numerous published studies which administered EPA
5 and/or DHA to observe their lipid effects in normal to high TG patients. A person of ordinary
6 skill in the art at the time of the invention would have understood that the results obtained in
7 studies conducted in normal, borderline-high or high TG patients (<500 mg/dL) would not be the
8 same as the lipid changes in patients with very-high TG levels (≥ 500 mg/dL).¹⁶⁴ Instead, persons
9 of ordinary skill in the art would have recognized that patients with very-high TG levels had
10 different lipid responses than patients with normal, border-high or high TG levels.

11 Furthermore, studies conducted in normal to high TG patients provided inclusive results
12 regarding EPA and DHA's differential on lipid parameters.¹⁶⁵ A person of ordinary skill in the

13 ¹⁶² *Id.*

14 ¹⁶³ See, e.g., Stalenhoef et al., *The Effect of Concentrated n-3 Fatty Acids Versus Gemfibrozil on Plasma*
15 *Lipoproteins, Low Density Lipoprotein Heterogeneity and Oxidizability in Patients with Hypertriglyceridemia*, 153
16 *ATHEROSCLEROSIS* 129, 134 (2000); Mori et al., *Purified eicosapentaenoic and docosahexaenoic acids have*
17 *differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic*
18 *men*, 71 *AM. J. CLIN. NUTRI.* 1085 (2000) ("Mori 2000").

17 ¹⁶⁴ Dunbar at 666 ("Most trials of lipid-lowering therapy were in patients with coronary heart disease who had
18 cholesterol abnormalities, and they often excluded patients with triglyceride levels over 300 mg/dL. Extending the
19 conclusions from such studies to patients with hypertriglyceridemia is fraught with error.")

19 ¹⁶⁵ Contacos et al., *Effect of Pravastatin and ω -3 Fatty Acids on Plasma Lipids and Lipoproteins in Patients with*
20 *Combined Hyperlipidemia*, 13 *ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY* 1755, 1756
21 (1993); Nozaki et al., *Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary*
22 *Hypercholesterolemia*, 62 *INT'L J. VITAMIN & NUTRITION RES.* 256 (1992); Geppert et al., *Microalgal*
23 *Docosahexaenoic Acid Decreases Plasma Triacylglycerol in Normolipidaemic Vegetarians: A Randomized Trial*, 95
24 *BRIT. J. NUTRITION* 779, 782-85 (2006); Matsuzawa et al., *Effect of Long-Term Administration of Ethyl*
25 *Icosapentate (MND-21) in Hyperlipidaemic Patients*, 7 *J. CLIN. THERAPEUTIC & MEDICINES* 1801 (1991)
26 (Defendants' Translation at ICOSAPENT_DFNDTS00006440); Leigh-Firbank et al., *Eicosapentaenoic acid and*
27 *docosahexaenoic acid from fish oils: differential associations with lipid responses*, 87 *BR. J. NUTR.* 435, 442
28 (2002); von Schacky 2006 ("The vast majority of these studies were performed with fish oils containing various
29 concentrations of EPA and DHA. Inherently, it was impossible to differentiate between the effects of the other fatty
30 acids present in the fish oils used and EPA and DHA, let alone EPA versus DHA."); U.S. Food and Drug

1 art would have been unable to conclude that there were real, significant, or discernable
2 differences between EPA and DHA in the normal to high TG patient population. For example,
3 the art was inconclusive regarding EPA and DHA's differential effects on lipid parameters;
4 many controlled studies indicated that DHA had little or no effect on LDL-C.¹⁶⁶ Most controlled
5 studies in patients with normal to high baseline TG levels indicated that DHA had little or no
6 effect on LDL-C.¹⁶⁷ Therefore, a person of ordinary skill would not have concluded that DHA
7 increases LDL-C in patients with normal to high baseline TG levels. In fact, many of these
8 studies concluded by stating there was a need for further research in order to elucidate the
9 mechanisms by which EPA and DHA impact lipid metabolism.¹⁶⁸

12 Administration, Center for Food Safety and Applied Nutrition, Clover Corporation Limited's GRAS notification for
13 Tuna Oil, January 15, 2002, *available at*
14 <https://www.fda.gov/downloads/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm258378.pdf>.
15 Weber 2000 ("In summary, the evidence indicates that both EPA and DHA have a marked hypotriglyceridemic
16 effect in humans. Differences in the effects of purified EPA and DHA on lipoprotein subfractions warrant further
17 clarification.").

18 ¹⁶⁶ See, e.g. Buckley *et al.*, *Circulating Triacylglycerol and ApoE Levels in Response to EPA and Docosahexaenoic*
19 *Acid Supplementation in Adult Human Subjects*, 92 BR. J. NUTR 477, 479-481 (2004); Conquer & Holub,
20 *Supplementation with an Algae Source of Docosahexaenoic Acid Increases (n-3) Fatty Acid Status and Alters*
21 *Selected Risk Factors for Heart Disease in Vegetarian Subjects*, 126 J. of Nutr. 3032-3039 (1996); Hamazaki *et al.*,
22 *Docosahexaenoic Acid-Rich Fish Oil Does Not Affect Serum Lipid Concentrations of Normolipidemic Young Adults*,
23 126 J. NUTR. 2784-2789 (1996); Grimsgaard *et al.*, *Highly Purified Eicosapentaenoic Acid and Docosahexaenoic*
24 *Acid in Humans Have Similar Triacylglycerol-Lowering Effects but Divergent Effects on Serum Fatty Acids*, 66 AM.
J. CLIN. NUTR. 649-59 (1997); Agren *et al.*, *Fish Diet, Fish Oil and Docosahexaenoic Acid Rich Oil Lower*
Fasting and Postprandial Plasma Lipid Levels, 50 EUROPEAN J. OF CLIN. NUTR. 765-771 (1997); Nestel *et al.*, *The*
n3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans, 76
AM. J. CLIN. NUTR. 326-30 (2002); Woodman *et al.*, *Effects of purified eicosapentaenoic and docosahexaenoic acids*
on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension, 76 AM.
J. CLIN. NUTR. 1007-15 (2002).

¹⁶⁷ Mori *et al.*, *The Independent Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Cardiovascular*
Risk Factors in Humans, 9 CURRENT OPINION CLINICAL NUTRITION & METABOLIC CARE 95, 98 (2006).
Moreover, Mori 2000 is the only study which compared EPA versus DHA, that is placebo controlled, which found
an increase in LDL-C after DHA administration.

¹⁶⁸ Leigh-Firbank at 443.

1 These studies, when taken as a whole, reflect the understanding at the time of the
2 invention: that EPA and DHA generally functioned in the same manner.¹⁶⁹ Therefore, they had
3 no impact on the way practitioners treated patients with severe hypertriglyceridemia. As
4 discussed above, review articles which provided guidance to practitioners for the treatment of
5 severe hypertriglyceridemia using omega-3 fatty acids did not differentiate between EPA and
6 DHA.¹⁷⁰

7 **IV. DESCRIPTION OF REFERENCES**

8 **A. General Overview**

9 The prior art publications disclosed by Defendants contain many deficiencies and would
10 ultimately be unpersuasive to a person of ordinary skill in the art. None of the prior art
11 references are directed to the very-high TG patient population, and many of them are not placebo
12 controlled and administer EPA, DHA, or both, in varying degrees of concentration.

13 Defendants attempt to improperly reserve the right to contest the ‘728 patent’s priority
14 claims with a single footnote in their contentions.¹⁷¹ This single statement is insufficient to set
15 forth the legal basis to challenge the priority date of the asserted patents. Therefore, Plaintiffs
16 have forfeited their right to contest the priority date of the asserted patents.¹⁷²

17 **1. Defendants Fail to Provide Studies Directed to the Very-High TG 18 Patient Population**

19 A person of ordinary skill at the time of the invention would *not* have used studies
20 conducted in normal to high TG patients (<500 mg/dL) to conclude that the observed lipid

22 ¹⁶⁹ See, e.g. Dunbar; Bays 2008 I; Harris 2008; Bays *in* Kwiterovich.

23 ¹⁷⁰ See e.g., Dunbar; Bays 2008 I; Harris 2008.

24 ¹⁷¹ Defendants’ Joint Invalidity Contentions at 24.

¹⁷² Plaintiffs do not even reserve the right to contest the priority date of the remaining asserted patents.

1 parameters would be the same in patients with very-high TG levels (≥ 500 mg/dL), because
2 patients with higher TG levels had different lipid responses compared to patients with lower TG
3 levels.

4 Until one tested the specific lipid lowering agent in patients with very-high triglycerides,
5 the lipid effects in this particular patient population could not be stated with any certainty based
6 solely on the effects in patients with lower TG levels. For example, fibrates and prescription
7 omega-3 therapies were two well-known drug classes used to treat patients with very-high
8 triglycerides at the time of the invention. Both classes had varying effects on TG and LDL-C
9 levels in patients, depending on patients' baseline TG levels.

10 A person of ordinary skill in the art did not expect to see an increase in LDL-C levels
11 when omega-3 fatty acids were administered to patients with normal, borderline-high or high TG
12 levels. In studies involving the borderline-high TG population (150-199 mg/dL),
13 Lovaza/Omacor significantly reduced TGs and raised HDL-C,¹⁷³ but had no significant effect on
14 other lipid-related variables, including LDL-C and Apo-B.¹⁷⁴ As discussed in Section III, the
15 increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering
16 TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct
17 consequence of TG lowering through increased VLDL particle conversion.¹⁷⁵ Because normal to
18 high TG patients do not have the large backlog of VLDL particles that very high TG patients

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20 ¹⁷³ Chan 2002 I at 2379-81.

21 ¹⁷⁴ *Id.* See also, Westphal at 918.

22 ¹⁷⁵ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
23 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
24 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.”).

1 have, a person of ordinary skill would not expect LDL-C to increase in normal to high TG
2 patients. It was also well known that the degree of LDL-C elevation observed with prescription
3 omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C
4 levels increased the most in patients with the highest baseline TG levels¹⁷⁶ and did not increase
5 for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that
6 EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

7 Defendants rely on a few studies which included a couple of subjects with baseline TG
8 levels ≥ 500 mg/dL. However, these studies included subjects with a wide range of baseline TG
9 levels, therefore a person of ordinary skill in the art could not draw conclusions related
10 specifically to the very-high TG patient population. Indeed, in these studies, the results from the
11 very-high TG patients were not separated from the rest of the study population such that a person
12 of ordinary skill could not draw such conclusions, even if desired. Furthermore, many of these
13 studies used a system of measurement called “Friedewald’s Equation” to calculate LDL-C levels,
14 which can only be used for patients with triglyceride levels < 400 mg/dL.¹⁷⁷ In addition, the
15 examiner agreed that the prior art did not disclose the claimed patient population of the asserted
16 patents.¹⁷⁸ Therefore, the LDL-C results in these studies do not include the very-high TG patient
17 population.

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¹⁷⁶ Bays 2008 I at 400-402.

22 ¹⁷⁷ See, e.g. Matsuzawa at ICOSAPENT_DFNDTS00006450.

23 ¹⁷⁸ See, e.g., ’594 Patent Reasons for Allowance; ’521 Patent Reasons for Allowance; ’225 Patent Reasons for
24 Allowance.

1 **3. Japanese Studies**

2 Some of the studies Defendants rely upon were Japanese publications.¹⁸² These studies
3 comprised Japanese patients only, tended to have small patient populations with a wide range of
4 baseline TG levels, administered low doses of Epadel with undisclosed concentration, and lacked
5 placebo control. Studies which contained only Japanese patients would not have been
6 extrapolated to Western populations because the Japanese consume a higher amount of EPA and
7 DHA in their diets. In fact, Defendants’ own reference states that the results from studies where
8 the patient population is exclusively Japanese cannot be generalized to other populations.¹⁸³ The
9 Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western
10 Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty
11 acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the
12 Japanese respond differently to lipid lowering agents than Westerners.

13 **4. Studies That Administered EPA and DHA in Varying Concentrations**

14 Many of the studies cited by Defendants administer EPA and/or DHA with low levels of
15 purity, making it difficult to ascribe an observed lipid effect specifically to the omega-3 fatty
16 acid administered.

17 A few of the studies administered DHA-enriched oils which comprised DHA and a
18 number of other saturated and polyunsaturated fatty acids.¹⁸⁴ A person of ordinary skill would
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¹⁸² See, e.g., Katayama; Matsuzawa; Takaku; Saito; Shinozaki.

21 ¹⁸³ Yokoyama *et al.*, Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients
22 (JELIS): a Randomized Open-Label, Blinded Endpoint Analysis, 369 LANCET 1090, 1097 (2007) (“Because our
population was exclusively Japanese, we cannot generalise our results to other populations.”).

23 ¹⁸⁴ See, e.g., Geppert; Maki *et al.*, *Lipid responses to a dietary docosahexaenoic acid supplement in men and women*
24 *with below average levels of high density lipoprotein cholesterol*, 24 J. AM. COL. NUTR. 189-99 (2005); Kelley *et al.*,
Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in hypertriglyceridemic

1 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
2 how much of the supplement's effects can be attributed to DHA.¹⁸⁵ For example, Defendants'
3 own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate,
4 may contribute to elevations in LDL-C.¹⁸⁶

5 Additionally, many of the studies administer Epadel without disclosing the purity of the
6 version of Epadel used. The purity of Epadel has varied over time and across different
7 formulations of the product, therefore it is difficult to determine the purity of the version of
8 Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that
9 Epadel was administered and assume that the composition comprised at least about 96%, by
10 weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted
11 claims. Nishikawa,¹⁸⁷ published in 1997, discloses a form of Epadel that was a 91% E-EPA
12 preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have
13 the requisite purity.¹⁸⁸

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20 *men*, 86 AM. J. CLIN. NUTR. 324-33 (2007); Ryan *et al.*, *Clinical Overview of Algal-Docosahexaenoic Acid: Effects on Triglyceride Levels and Other Cardiovascular Risk Factors*, 16 AM. J. THERAPEUTICS 183-192 (2009).

21 ¹⁸⁵ See Mori 2006 at 96.

22 ¹⁸⁶ Maki at 197.

23 ¹⁸⁷ Nishikawa *et al.*, *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 ¹⁸⁸ See also, Ando at 2177 (Epadel® with purity greater than 91%), Nakamura at 23 (Epadel ® with purity > 90%).

1 **5. Studies which administered only EPA or only DHA**

2 Many of the studies cited by Defendants administered only EPA¹⁸⁹ or only DHA¹⁹⁰ and
3 studied its lipid effects. These types of studies fail to provide a head to head comparison of EPA
4 versus DHA. Therefore, a person of ordinary skill in the art would not rely on EPA-only or
5 DHA-only studies to draw any conclusions related to possible differences between the lipid
6 effects of EPA and DHA.

7 **B. Summary of Prior Art References¹⁹¹**

8 **1. WO ‘118¹⁹²**

9 WO ’118 is directed to a composition containing EPA for the purpose of preventing the
10 occurrence of cardiovascular events in multiple risk patients. It was considered by the USPTO
11 during prosecution of the asserted patents. Defendants contend that WO ’118 discloses the
12 administration of highly-purified ethyl-EPA to persons with hypertriglyceridemia.¹⁹³

13 WO ’118 does not disclose administration of highly-purified ethyl-EPA to the target
14 population of the claimed invention. The claimed invention is directed to persons with severe
15 hypertriglyceridemia (i.e. TG levels above 500 mg/dL). WO ’118, on the other hand, is directed
16 towards hypercholesterolemia patients, “in particular, in preventing occurrence of cardiovascular
17

18 ¹⁸⁹ See, e.g., Katayama, Matsuzawa, Takaku, Saito, Yokoyama (w/ statin), Satoh, Shinozaki, Ando, Hayashi, Mataka
19 (w/ statin), Nakamura, Nozaki, Okumura.

20 ¹⁹⁰ See, e.g., Maki, Geppert, Kelley, Theobald *et al.*, *LDL cholesterol raising effect of low dose docosahexaenoic
acid in middle-aged men and women*, 79 AM. J. CLIN. NUTR. 558-63 (2004).

21 ¹⁹¹ For WO ‘118, Katayama, Matsuzawa, Shinozaki, and Takaku, Plaintiffs relied on the English translations
22 provided by Defendants. For these and any other translations of references provided by Defendants, Plaintiffs
reserve their rights to use a certified translation of these prior art references and to dispute any alleged disclosure of
these references that may have been incorrectly translated by Defendants.

23 ¹⁹² PCT Pub. App. WO 2007/142118 (“WO ’118”) (published Dec. 13, 2007).

24 ¹⁹³ Defendants’ Joint Invalidity Contentions at 43.

1 events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer
2 from the risk of cardiovascular events.”¹⁹⁴ The patient only optionally may have TG levels of at
3 least 150 mg/dL.¹⁹⁵ Further, WO ’118’s emphasis on reducing cardiovascular events suggests
4 that its disclosure is directed to patients with borderline-high to high TG levels; the primary goal
5 for patients with very-high TG is not to reduce cardiovascular events, but to prevent acute
6 pancreatitis by decreasing TG levels.¹⁹⁶

7 WO ’118 does not distinguish EPA from DHA when discussing the effectiveness of the
8 composition for treating hypertriglyceridemia.¹⁹⁷ WO ’118 states that “[a]nother preferable fatty
9 acid . . . is DHA-E,” and that “the compositional ratio of EPA-E/DHA-E, content of EPA-E and
10 DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited
11 as long as intended effects of the present invention are attained.”¹⁹⁸ It further states that “the
12 composition is preferably the one having a high purity of EPA-E and DHA-E.”¹⁹⁹

13 Moreover, WO ’118 does not disclose EPA’s effect on LDL-C, VLDL-C, Apo-B, or Lp-
14 PLA2.

15 2. WO ’900²⁰⁰

16 WO ’900 was published in 2006. The publication is directed at a process of producing
17 purified EPA from a culture of micro-organisms. It was considered by the USPTO during
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19 ¹⁹⁴ WO ’118 at 9.

20 ¹⁹⁵ *Id.* at 8.

21 ¹⁹⁶ *See* Section III.

22 ¹⁹⁷ WO ’118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective
component”).

23 ¹⁹⁸ *Id.* at 22-23.

24 ¹⁹⁹ *Id.* at 23.

²⁰⁰ PCT Pub. App. WO 2008/004900 (“WO ’900”) (published Jan. 10, 2008).

1 prosecution of the asserted patents. Defendants argue that the publication “teaches the
2 administration of pure EPA containing no DHA and that the presence of impurities, including
3 DHA can reduce the effectiveness of EPA.”²⁰¹

4 WO ‘900 only discloses the method of producing purified EPA for therapeutic use, it
5 does not teach *administration* of pure EPA. WO ‘900 has no discussion, for example, about the
6 target population, dose, duration, or method of treatment.

7 WO ‘900 does not teach administration of pure EPA to treat hypertriglyceridemia. It
8 lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one
9 of them.²⁰² Moreover, WO ‘900 does not teach the desired effect of EPA other than commenting
10 generally that it “may promote health and ameliorate or even reverse the effects of a range of
11 common diseases.”²⁰³ It has no discussion, for example, on any TG-lowering effect of EPA.

12 WO ‘900 does not identify the specific undesired effect of DHA or other impurities it is
13 trying to prevent other than commenting generally that “the desired effects of EPA may be
14 limited or reversed” by them.²⁰⁴ It has no discussion related to any LDL-C effects caused by
15 DHA.

16 Therefore, a person of ordinary skill would not have been motivated to use the purified
17 EPA disclosed in WO ‘900 to treat hypertriglyceridemia.

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²⁰¹ Defendants’ Joint Invalidity Contentions at 213.

22 ²⁰² See, e.g., ‘900 Pub. at 16-17.

23 ²⁰³ *Id.* at 5.

24 ²⁰⁴ *Id.* at 39.

1 **3. Agren²⁰⁵**

2 Agren investigated how moderate amounts of *n*-3 fatty acids in different forms affect
3 fasting and postprandial lipid and lipoprotein concentrations. Subjects were randomly allocated
4 into control, fish diet, fish oil and DHA-oil groups. The study period was 15 weeks. The
5 subjects in the fish diet group ate fish containing meals which provided approximately 380 mg
6 EPA and 670 mg DHA per day. Those in the fish oil group were administered 4 g of fish oil per
7 day, which provided 1.33 g EPA and 0.95 g DHA per day. Those in the DHA-oil group took 4 g
8 of DHA-oil, which provided 1.68 g of DHA per day.

9 Agren found that fasting plasma triglyceride decreased in all study groups, and “[m]ost of
10 this decrease took place in VLDL triglycerides.”²⁰⁶ Agren states that “the decrease of
11 triglycerides compared to the dose of DHA given does not indicate any great difference in the
12 effect of EPA and DHA on serum total or VLDL triglycerides.”²⁰⁷

13 Agren states that “[i]n accordance with earlier results, a moderate *n*-3 fatty acid intake in
14 the present study did not show any significant changes in LDL cholesterol concentrations,
15 although a slight increasing tendency was seen in the fish diet and fish oil groups.”²⁰⁸ On the
16 other hand, “[n]o tendency to increased LDL cholesterol was seen in the DHA-oil group.”²⁰⁹
17 Moreover, “the HDL to LDL cholesterol ratio was increased only in this group.”²¹⁰

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20 ²⁰⁵ Agren *et al.*, *Fish Diet, Fish Oil and Docosahexaenoic Acid Rich Oil Lower Fasting and Postprandial Plasma Lipid Levels*, 50 EUROPEAN J. OF CLIN. NUTR. 765-771 (1997).

21 ²⁰⁶ *Id.* at 767-68; Table 2.

22 ²⁰⁷ *Id.* at 768.

23 ²⁰⁸ *Id.* at 769.

24 ²⁰⁹ *Id.* at 770.

²¹⁰ *Id.*

1 **4. Ando**²¹¹

2 In Ando, 1.8 g/day of 91% pure EPA was administered for three months to dialysis
3 patients. The average baseline triglyceride level of the subjects was 258 mg/dL. After treatment,
4 there was a significant reduction in Ox-LDL (oxidized LDL) and triglycerides in the EPA group
5 compared to the placebo group. Ando was considered by the USPTO during prosecution of the
6 patents at issue.

7 Defendants contend that Ando shows marked reduction in triglyceride and LDL levels
8 after three-month treatment.²¹² Defendants also contend that Ando teaches that “EPA treatment
9 significantly reduced plasma levels of remnant lipoproteins and ox-LDL without inducing
10 adverse reactions in the dialysis patients,” and that “this reduction was accompanied by
11 qualitative changes in lipoproteins that could contribute to the prevention of atherosclerosis.”²¹³

12 Ando does not show reduction in LDL-C. Ando measured ox-LDL levels, not LDL-C.
13 Ando concludes that it is likely that “EPA is involved in part in the prevention of LDL
14 peroxidation.”²¹⁴ As such, Ando suggests that EPA reduces ox-LDL by suppressing conversion
15 of LDL-C to ox-LDL, not by reducing LDL-C. Therefore, a person of ordinary skill would not
16 have expected that EPA reduces LDL-C based on Ando.

17 A person of ordinary skill would not have been motivated to use EPA instead of fish oil
18 or DHA based on Ando. Ando does not teach that any health benefit seen in the study was
19 exclusive to EPA and not shared with fish oil or DHA. Based on the understanding in art at the
20

21 ²¹¹ Ando *et al.*, *Eicosapentaenoic Acid Reduces Plasma Levels of Remnant Lipoproteins and Prevents in Vivo*
Peroxidation of LDL in Dialysis Patients, 10 J. AM. SOC. NEPHROL. 2177-84 (1999) (“Ando”).

22 ²¹² Defendants’ Joint Invalidity Contentions at 185.

23 ²¹³ *Id.*

24 ²¹⁴ Ando at 2183.

1 time, a person of ordinary skill would have expected the results to be applicable to fish oil and
2 DHA as well.²¹⁵ Therefore, a person of ordinary skill would not have been motivated to use
3 EPA to treat hypertriglyceridemia based on Ando.

4 Furthermore, Ando does not disclose all of the limitations of the claimed invention. For
5 example, the study was conducted in patients with <500 mg/dL baseline TG levels; the purity of
6 EPA is only 91%; only 1.8 g/day was administered; and the DHA content is unknown.

7 5. Calabresi²¹⁶

8 Calabresi investigated the ability of Omacor to favorably correct plasma lipid/lipoprotein
9 levels and LDL particle distribution in patients with familial combined hyperlipidemia. The
10 patients received four capsules of Omacor (providing 3.4 g of EPA and DHA per day) or placebo
11 for 8 weeks in a randomized, double-blind, cross-over study.

12 Defendants contend that Calabresi shows administration of fish oil-based
13 pharmaceuticals to patients with TG above 500 mg/dL.²¹⁷ Defendants contend that Calabresi
14 shows that administration of Omacor significantly lowered plasma triglycerides and VLDL-C
15 levels.²¹⁸ Defendants contend that Calabresi shows that administration of Omacor increased
16 LDL-C and Apo-B levels.²¹⁹

17 Calabresi provides no motivation to use purified EPA instead of DHA. First, Calabresi
18 did not differentiate EPA and DHA. Calabresi states that “[t]here is general agreement that
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20 ²¹⁵ See Section III.

21 ²¹⁶ Calabresi *et al.*, *Omacor in Familial Combined Hyperlipidemia: Effects on Lipids and Low Density Lipoprotein*
Subclasses, 148 *ATHEROSCLEROSIS* 387-96 (2000) (“Calabresi”).

22 ²¹⁷ Defendants’ Joint Invalidation Contentions at 174-75.

23 ²¹⁸ *Id.* at 175.

24 ²¹⁹ *Id.*

1 hypertriglyceridemic patients respond to *n*-3 FAs administration with consistent reductions in
2 plasma triglyceride and VLDL levels.”²²⁰ It also states that “*n*-3 FAs appear to exert their
3 primary effect on lipoprotein metabolism by decreasing hepatic triglyceride synthesis.”²²¹

4 Second, Calabresi shows that Omacor’s LDL-C effect was potentially antiatherogenic. It
5 states that “[t]he effects of Omacor on the plasma lipid/lipoprotein profile, with a decrease in the
6 number of circulating VLDL particles and a shift from dense LDL particles to buoyant LDL, i.e.
7 possibly indicative of a less atherogenic LDL profile.”²²²

8 Third, a person of ordinary skill would not have compared the data from Calabresi with
9 studies administering EPA only, to draw a conclusion on differential therapeutic effects between
10 EPA and DHA. Calabresi shows that “[p]lasma triglycerides and LDL-cholesterol showed
11 considerable individual variation in response to Omacor treatment.”²²³

12 Moreover, there was no reasonable expectation of success in achieving the claimed
13 invention based on Calabresi. Calabresi shows that LDL-C increase is correlated to the baseline
14 lipid parameters of the patients. Calabresi states that “[t]he LDL-cholesterol rise correlated
15 significantly and positively with baseline triglycerides ($r=0.571$) and VLDL-C ($r=0.538$), and
16 negatively with baseline LDL-cholesterol/Apo-B ratio ($r=0.659$) and LDL size ($r=0.645$).”²²⁴ As
17 such, a person of ordinary skill would have expected that LDL-C would increase in patients with
18 TG above 500 mg/dL regardless of the treatment method.

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20 _____
21 ²²⁰ Calabresi at 393.

22 ²²¹ *Id.*

23 ²²² *Id.* at 394.

24 ²²³ *Id.* at 393.

²²⁴ *Id.* at 392.

1 **6. Chan 2002 II**²²⁵

2 In Chan 2002 II, a 6-week randomized, placebo-controlled , 2 x 2 factorial intervention
3 study of atorvastatin (40 mg / day) and fish oil (4 g per day) was conducted on 52 obese men
4 with dyslipidemia and insulin resistance. Administration of fish oil resulted in a statistically
5 significant decrease in TG levels and non-significant effects on LDL-C, Apo-B, and non-HDL-
6 C.²²⁶

7 Defendants contend that Chan 2002 II shows administration of 4 grams of a mixture of
8 EPA and DHA.²²⁷ Defendants contend that Chan 2002 II shows that DHA was reported to
9 increase LDL-C levels while products containing only EPA did not.²²⁸ Defendants contend that
10 Chan 2002 II shows that there was a reasonable expectation that a composition comprising EPA,
11 but not DHA, would lower non-HDL-C levels.²²⁹ Defendants contend that Chan 2002 II show
12 that it was known that EPA and DHA had different effects on lipid metabolism as compared to
13 one another.²³⁰

14 Chan 2002 II does not show administration of 4 grams of a mixture of EPA and DHA to
15 patients with TG above 500 mg/dL. The starting baseline TG level for the fish oil group was
16 only 177 mg/dL. Therefore, Chan 2002 II does not provide a motivation or a reasonable
17 expectation of success for administering 4 grams of EPA to patients with TG above 500 mg/dL.
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20 ²²⁵ Chan *et al.*, *Factorial study of the effects of atorvastatin and fish oil on dyslipidaemia in visceral obesity*, 32
EUROPEAN JOURNAL OF CLINICAL INVESTIGATION 429-36 (2002) (“Chan 2002 II”).

21 ²²⁶ Chan 2002 II at 433, Table 3.

22 ²²⁷ Defendants’ Joint Invalidity Contentions at 215.

23 ²²⁸ *Id.*

23 ²²⁹ *Id.* at 229.

24 ²³⁰ *Id.* at 208, 258.

1 Chan 2002 II also does not show that a person or ordinary skill expected DHA to increase
2 LDL-C while products containing only EPA would not. To the contrary, in Chan 2002 II,
3 administration of fish oil caused a non-significant effect on LDL-C.

4 Chan 2002 II does not show that there was a reasonable expectation that a composition
5 comprising EPA, but not DHA, would lower non-HDL-C levels. To the contrary, in Chan 2002
6 II, administration of fish oil caused a non-significant effect on non-HDL-C.

7 Chan 2002 II does not show that it was known that EPA and DHA had different effects
8 on lipid metabolism as compared to one another. Chan 2002 II does not study EPA and DHA
9 separately. In fact Chan 2002 II is concerned with the therapeutic efficacy of fish oil, stating that
10 “[p]lasma EPA and DHA concentrations also increased . . ., confirming therapeutic compliance
11 with fish oil capsules.”²³¹

12 7. Chan 2003²³²

13 The purpose of Chan 2003 was to study the effect of fish oils on the metabolism of Apo-
14 B and chylomicron remnants in obese men. Twenty-four dyslipidemic, viscerally obese men
15 were randomly assigned to receive either fish oil capsules (4 g/day, consisting of 45% EPA and
16 39% DHA) or matching placebo (corn oil, 4 g/day) for 6 weeks. Administration of fish oil
17 resulted in a statistically significant decrease in TG levels and non-significant effects on total
18 cholesterol, HDL-C, Non-HDL-C, LDL-C and Apo-B.²³³

21 ²³¹ Chan 2002 II at 431.

22 ²³² Chan *et al.*, *Randomized controlled trial of the effect of n-3 fatty acid supplementation on the metabolism of*
23 *apolipoprotein B-100 and chylomicron remnants in men with visceral obesity*, 77 AM. J. CLIN. NUTR. 300-07 (2003)
24 (“Chan 2003”).

²³³ Chan 2003 at 303, Table 2.

1 Defendants contend that Chan 2003 shows that it was known that EPA and DHA had
2 different effects on lipid metabolism as compared to one another.²³⁴ Defendants contend that
3 Chan 2003 shows administration of 4 grams of a mixture of EPA and DHA.²³⁵ Defendants
4 contend that Chan 2003 shows that DHA was reported to increase LDL-C levels while products
5 containing only EPA did not.²³⁶ Defendants contend that Chan 2003 shows that there was a
6 reasonable expectation that a composition comprising EPA, but not DHA, would lower non-
7 HDL-C levels.²³⁷

8 Chan 2003 does not show administration of 4 grams of a mixture of EPA and DHA to
9 patients with TG above 500 mg/dL. The baseline TG level for the fish oil group was only 177
10 mg/dL. Therefore, Chan 2003 does not provide a motivation or a reasonable expectation of
11 success for administering 4 grams of EPA to patients with TG above 500 mg/dL.

12 Chan 2003 does not show that a person of ordinary skill expected DHA to increase LDL-
13 C while products containing only EPA would not. To the contrary, in Chan 2003, administration
14 of fish oil caused a non-significant effect on LDL-C.

15 Chan 2003 does not show that there was a reasonable expectation that a composition
16 comprising EPA, but not DHA, would lower non-HDL-C levels. To the contrary, in Chan 2003,
17 administration of fish oil caused a non-significant effect on non-HDL-C.

18 Chan 2003 does not show that it was known that EPA and DHA had different effects on
19 lipid metabolism as compared to one another. Chan 2003 attributes a common mechanisms for
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21 ²³⁴ Defendants' Joint Invalidity Contentions at 208, 258.

22 ²³⁵ *Id.* at 215.

23 ²³⁶ *Id.*

24 ²³⁷ *Id.* at 230.

1 the TG-lowering mechanism of omega 3 fatty acids generally, stating that “[s]tudies in animals
2 and humans have shown that the hypotriacylglycerolemic effect of n-3 fatty acids primarily
3 involves the suppression of hepatic VLDL Apo-B production.”²³⁸ It also states that “other
4 studies have shown that enrichment of n-3 fatty acids in VLDL particles favor the conversion of
5 VLDL to LDL.”²³⁹

6 **8. Childs²⁴⁰**

7 Childs investigated whether the ratio of EPA and DHA in fish oil had an effect on plasma
8 lipid responses. It fed eight normolipidemic men three diets per day enriched in butter fat, EPA-
9 rich pollock oil, or either DHA-rich tuna or DHA-rich salmon-blend oil.

10 Both the EPA-rich and DHA-rich diets resulted in a statistically significant decrease in
11 TG levels. The DHA-rich tuna and salmon diets resulted in a statistically significant decrease in
12 LDL-C and Apo-B, while the EPA-rich pollock diet cause a statistically significant increase in
13 Apo-B and a nonsignificant effect on LDL-C.²⁴¹ As a result, Childs states that “there may be a
14 second, selective effect of DHA that causes the lowering of LDL.”²⁴²

15 HDL-C decreased more in the EPA-rich pollock group than in the EPA-rich tuna and
16 salmon groups.²⁴³ As a result, LDL-C: HDL-C was lower in the DHA-rich tuna and salmon

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²³⁸ Chan 2003 at 305.

20 ²³⁹ *Id.* at 306.

21 ²⁴⁰ Childs *et al.*, *Divergent Lipoprotein Responses to Fish Oils With Various Ratios of Eicosapentaenoic Acid and Docosahexaenoic Acid*, 52 AM. J. CLIN. NUTR. 632-39 (1990) (“Childs”).

22 ²⁴¹ *Id.* at Table 5.

23 ²⁴² *Id.* at 637.

24 ²⁴³ *Id.* at Table 6.

1 groups compared to the EPA-rich pollock group, “suggesting a lesser risk for heart disease on the
2 tuna- and salmon-oil diets than on the pollock-oil diet.”²⁴⁴

3 9. Conquer 1996²⁴⁵

4 Conquer 1996’s purpose was to investigate the influence of dietary supplementation with
5 an algae source of DHA, devoid of any EPA, on serum/platelet DHA status, the estimated
6 retroconversion of DHA to EPA, and risk factors for heart disease.²⁴⁶ The subjects were 24
7 healthy vegetarians. The DHA group received 1.62 g/day of DHA. The control group received
8 vegetable oil. Serum lipid and lipoprotein levels were measured at three weeks and six weeks.
9 The DHA group exhibited a statistically significant reduction in TG levels; however, there was
10 no significant change in total cholesterol or LDL-C with DHA supplementation. The study also
11 found that “part of the cardioprotective effect of fish/fish oil containing (n-3) PUFA appears due
12 to DHA in addition to EPA.”²⁴⁷ The study concludes that “the consumption of 1.62 g of an
13 animal-free source of DHA per day by vegetarians readily enhances their DHA status, provides
14 for EPA formation based on serum and platelet phospholipid analysis, and exerts moderately
15 favorable (lowering) effects on the total cholesterol: HDL-cholesterol ratio, as well as serum
16 triglyceride concentrations.”²⁴⁸

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20 ²⁴⁴ *Id.* at 637.

21 ²⁴⁵ Conquer & Holub, *Supplementation with an Algae Source of Docosahexaenoic Acid Increases (n-3) Fatty Acid
22 Status and Alters Selected Risk Factors for Heart Disease in Vegetarian Subjects*, 126 J. NUTR. 3032-39 (1996)
23 (“Conquer 1996”).

24 ²⁴⁶ *Id.* at 3032.

²⁴⁷ *Id.* at 3038.

²⁴⁸ *Id.*

1 **10. Contacos**²⁴⁹

2 The aim of Contacos study was to determine the safety and efficacy of pravastatin and
3 fish oil (himega), separately and in combination, for management of patients with mixed
4 hyperlipidemia and evaluate their effects on VLDL and LDL. Patients were administered a
5 single drug therapy (pravastatin or himega) for the first six weeks, and then subjects who had not
6 achieved desirable lipid effects (TC < 201 mg/dL and TG < 177 mg/dL) were placed on
7 combined drug therapy for 12 weeks (no placebo during combined treatment phase). The fish oil
8 group was administered 6 g of himega daily, which contained 2 g of EPA and 1 g of DHA.
9 Contacos was considered by the USPTO during prosecution of the patents at issue.

10 Contacos discloses administration of fish oil, pravastatin, and combination of fish oil and
11 pravastatin, but it does not disclose administration of highly purified EPA. Contacos
12 demonstrated that fish oil caused a reduction in TG levels.²⁵⁰ Contacos also showed that fish oil
13 did not increase LDL-C or Apo-B significantly when administered to patients with triglycerides
14 less than 500 mg/dL.²⁵¹ Contacos notes that “[f]ish oils rich in the ω-3 fatty acids,
15 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to effectively
16 reduce TG levels, but their effect on LDL is inconsistent.”²⁵² Therefore, Contacos does not
17 disclose or suggest any differential effects between EPA and DHA, and refers generically to
18 “fish oil” and concludes that pravastatin--not fishoil--“decreased LDL-C, thereby reversing the
19 elevation in LDL-C associated with fish oil therapy.”

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21 ²⁴⁹ Contacos *et al.*, *Effect of Pravastatin and ω-3 Fatty Acids on Plasma Lipids and Lipoproteins in Patients with*
Combined Hyperlipidemia, 13 *ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY* 1755 (1993) (“Contacos”).

22 ²⁵⁰ *Id.* at 1756.

23 ²⁵¹ *Id.*

24 ²⁵² *Id.*

1 **11. Geppert²⁵³**

2 In Geppert, 2.28 g/day of DHA-rich oil (providing 0.94 g/day DHA) derived from
3 microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. The subjects
4 consisted of 87 females and 27 males. The study was conducted as a randomized double-blind,
5 placebo-controlled study, and fasting blood samples were obtained before and after the
6 administration period. Geppert was considered by the USPTO during prosecution of the patents
7 at issue.

8 Defendants contend that Geppert teaches that administration of DHA decreases
9 triglycerides while increasing LDL and HDL cholesterol concentrations.²⁵⁴

10 A person of ordinary skill would not have been convinced that DHA increases LDL-C
11 based on Geppert. As Geppert acknowledges, prior studies have shown “[i]nconsistent effects of
12 DHA on LDL cholesterol.”²⁵⁵ Rather than reading Geppert in isolation, a person of ordinary
13 skill would have read Geppert together with the prior studies cited in Geppert. As such, a person
14 of ordinary skill would have concluded that there was confusion in the art and it was unclear
15 whether DHA increased LDL-C.²⁵⁶ Further, the DHA-rich oil contained other saturated and
16 polyunsaturated fatty acids. As such, Geppert does not disclose the independent effects of DHA,
17 because it is not clear how much of the supplement’s effects can be attributed solely to DHA.²⁵⁷

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²⁵³ Geppert *et al.*, *Microalgal Docosahexaenoic Acid Decreases Plasma Triacylglycerol in Normolipidaemic Vegetarians: A Randomized Trial*, 95 BRIT. J. NUTRITION 779 (2006) (“Geppert”).

21 ²⁵⁴ Defendants’ Joint Invalidity Contentions at 75.

22 ²⁵⁵ Geppert at 784.

23 ²⁵⁶ See also Section III.

24 ²⁵⁷ See Mori 2006 at 96.

1 A person of ordinary skill would have expected that Geppert's results would be
2 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
3 was the only component of fish oil to increase LDL. For example, there is no data comparing
4 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying to
5 explain the mechanism of LDL-C increase.²⁵⁸ A person of ordinary skill would not have
6 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

7 Furthermore, Geppert's study lasted only 8 weeks, which is 33% shorter than the claimed
8 limitation of 12 weeks.

9 12. Grimsgaard²⁵⁹

10 Defendants rely on Grimsgaard to demonstrate the "known clinical benefits of
11 administering pure EPA - lowering triglycerides without raising LDL-C."²⁶⁰ Grimsgaard
12 examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with
13 normal triglyceride levels for 7 weeks. Grimsgaard was considered by the USPTO during
14 prosecution of the patents at issue.

15 The results from the Grimsgaard study show that both DHA and EPA reduce
16 triglycerides in individuals with normal triglyceride levels. The authors state that the net
17 decrease in triglycerides was consistently greater for DHA. Grimsgaard concludes that DHA
18 may be responsible for the increase in HDL-C observed with some n-3 fatty acid supplements,
19 which is consistent with previous studies which "suggested that serum HDL-C is better
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21 ²⁵⁸ Geppert at 784.

22 ²⁵⁹ Grimsgaard *et al.*, *Highly Purified Eicosapentaenoic Acid and Docosahexaenoic Acid in Humans Have Similar*
23 *Triacylglycerol-Lowering Effects but Divergent Effects on Serum Fatty Acids*, 66 AM. J. CLIN. NUTR. 649-59 (1997)
24 ("Grimsgaard").

²⁶⁰ Defendants' Joint Invalidity Contentions at 206.

1 maintained with oil rich in DHA than oil rich in EPA.”²⁶¹ Although Grimsgaard states that EPA
2 may produce a small decrease in serum total cholesterol, it does not specifically comment on
3 EPA’s effect on LDL-C.

4 Defendants state that “Grimsgaard discloses that administration of DHA alone resulted in
5 an increase in LDL-C.”²⁶² This statement is false. The administration of DHA resulted in a
6 nominal increase in LDL-C which was not statistically significant. In fact, Table 4 demonstrates
7 that EPA and DHA’s impact on LDL-C was the same as the effect of the placebo corn oil group;
8 that is, there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Table
9 4 also demonstrates that despite a statistically significant decrease in Apo-B **compared to**
10 **baseline** for EPA, statistical significance was not reached when EPA is compared to placebo.
11 Therefore, there was no difference between EPA, DHA, or placebo’s effect on Apo-B levels.
12 This discrepancy demonstrates the importance of placebo controlled studies; although a
13 statistically significant effect may be observed when compared to baseline levels, one must
14 compare it against placebo to prove that the change is linked to EPA or DHA.

15 13. Hamazaki²⁶³

16 Hamazaki investigated the effects of DHA-rich fish oil on blood lipid concentrations.
17 Subjects took either DHA-rich fish oil capsules containing 1.5-1.8 g DHA, or control capsules
18 containing 97% soybean oil and 3% fish oil for 13 weeks. There was no significant changes in
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²⁶¹ Grimsgaard at 654.

22 ²⁶² Defendants’ Joint Invalidation Contentions at 79 and 184.

23 ²⁶³ Hamazaki *et al.*, *Docosahexaenoic Acid-Rich Fish Oil Does Not Affect Serum Lipid Concentrations of*
24 *Normolipidemic Young Adults*, 126 J. NUTR. 2784-89 (1996) (“Hamazaki”).

1 the DHA group for the following serum lipids: total cholesterol, HDL-C, LDL-C, TG or Apo-
2 B.²⁶⁴

3 **14. Hayashi²⁶⁵**

4 In Hayashi, 1.8 g/day of EPA (purity unknown) was administered to 28 patients for 8
5 weeks. The average triglyceride level of the patients before the administration was 300 mg/dL.
6 Hayashi was considered by the USPTO during prosecution of the patents at issue.

7 Defendants contend that Hayashi shows that it was known that purified EPA has been
8 administered to patients with triglyceride levels above 500 mg/dL.²⁶⁶ Defendants contend that
9 Hayashi discloses reduction in triglyceride, LDL-C, and Apo-B.²⁶⁷ Defendants contend that
10 Hayashi discloses that EPA might have antiatherogenic effects on plasma lipid profile.²⁶⁸

11 A person of ordinary skill would not have been convinced that Hayashi discloses
12 administration of purified EPA to patients with triglyceride levels above 500 mg/dL. It is true
13 that Table I says that triglyceride level was 300 +/- 233 mg/dL at week 0.²⁶⁹ The standard error
14 of +/- 233 mg/dL is unusually high, and there is no explanation in Hayashi for such a high
15 standard error. In fact, the correlation graphs in Figure 2 show no subject with triglyceride level
16 greater than 400 mg/dL, which is incompatible with the high standard error in Table I.²⁷⁰ As

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²⁶⁴ *Id.* at 2786.

20 ²⁶⁵ Hayashi *et al.*, *Decreases in Plasma Lipid Content and Thrombotic Activity by Ethyl Icosapentate Purified from*
Fish Oils, 56(1) CURR. THERAP. RES. 24-31 (1995) (“Hayashi”).

21 ²⁶⁶ Defendants’ Joint Invalidity Contentions at 210.

22 ²⁶⁷ *Id.* at 81.

23 ²⁶⁸ *Id.*

24 ²⁶⁹ Hayashi at 26.

²⁷⁰ *Id.* at 28.

1 such, a person of ordinary skill would not have been convinced that the study actually included
2 subjects with triglycerides above 500 mg/dL.

3 A person of ordinary skill would not have found the results of Hayashi reliable. The
4 study involved only 28 patients, and it was conducted for only 8 weeks. Furthermore, the study
5 was conducted exclusively with Japanese patients and was not placebo controlled. Without
6 placebo, one cannot distinguish between the effect of the placebo from that of the active agent.
7 If there were subjects with triglycerides above 400 mg/dL, the Friedewald equation that was used
8 would not have been suitable for estimating LDL-C for those subjects. Furthermore, Hayashi
9 shows that changes in Apo-B and LDL-C were not statistically significant.²⁷¹

10 A person of ordinary skill would have expected that the teachings of Hayashi were
11 applicable to DHA and fish oil in general, and not limited to EPA. Hayashi does not show that
12 EPA is the only component of fish responsible for lowering triglyceride. Hayashi does not show
13 that DHA or fish oil would increase LDL-C. In fact, Hayashi concludes that EPA may have
14 antiatherogenic effects because it reduces total cholesterol and triglycerides,²⁷² and it goes on to
15 explain that “the mechanism by which N-3 fatty acids in fish oil decrease plasma cholesterol and
16 triglyceride content is well documented.”²⁷³ Therefore, a person of ordinary skill reading
17 Hayashi would not have been motivated to treat hypertriglyceridemia with purified EPA as
18 opposed to fish oil or DHA.

22 ²⁷¹ *Id.* at 26, Table I.

23 ²⁷² *Id.* at 28.

24 ²⁷³ *Id.* at 30.

1 Furthermore, Hayashi does not disclose all of the limitations of the claimed invention.
2 For example, purity of EPA that was administered in Hayashi is unknown and it is unclear how
3 much DHA was contained in the drug.

4 **15. Katayama²⁷⁴**

5 Defendants rely on Katayama to demonstrate the “known clinical benefits of
6 administering pure EPA - lowering triglycerides without raising LDL-C.”²⁷⁵ However,
7 Katayama was directed to an investigation of the safety and efficacy of Epadel during long term
8 treatment in patients with hyperlipidemia and was not placebo controlled.²⁷⁶ Without placebo,
9 one cannot distinguish between the effect of the placebo from that of the active agent. Notably,
10 Katayama does not disclose any LDL-C related data or describe any LDL-C effects. The only
11 results disclosed by Katayama were a significant reduction in triglycerides and total cholesterol
12 when Epadel is administered to patients with borderline-high to high triglyceride levels, and its
13 safety for long term use in this patient population.²⁷⁷ Katayama was considered by the USPTO
14 during prosecution of the patents at issue.

15 Katayama does not disclose the purity of the Epadel used in the study. The purity of
16 Epadel has varied over time and across different formulations of the product, therefore it is
17 difficult to determine the purity of the version of Epadel® used unless it is specified by the
18 disclosure. One cannot simply rely on the fact that Epadel® was administered and assume that
19 the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
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21 ²⁷⁴ Katayama *et al.*, *Efficacy And Safety Of Ethyl Icosapentate (Epadel®) Given For A Long Term Against*
Hyperlipidemia, 21 PROG. MED. 457 (2001) (“Katayama”).

22 ²⁷⁵ Defendants’ Joint Invalidity Contentions at 206.

23 ²⁷⁶ Katayama at 2.

24 ²⁷⁷ *Id.* at 16.

1 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
2 disclosing the purity of the form of Epadel® used in the Katayama study. Nishikawa,²⁷⁸
3 published in 1997, discloses a form of Epadel® that was a 91% E-EPA preparation. Nishikawa
4 reflects that versions of Epadel® used in some clinical studies do not have the requisite purity.

5 Katayama administered 1.8 g/day of Epadel to patients with normal triglyceride levels,
6 and 2.7 g/day to patients with abnormal triglyceride levels (≥ 150 mg/dL).²⁷⁹ The average
7 baseline value for all patients was 226.7 mg/dL, and the average baseline value for patients with
8 abnormal triglyceride levels (≥ 150 mg/dL) was 279.2 mg/dL.

9 Therefore, Katayama discloses administration of the wrong dose of Epadel, the purity of
10 which is unknown, to the wrong patient population, the majority of whom are on concomitant
11 drugs which may have affected the results of the study. There is no discussion related to the
12 LDL-C impact of the Epadel administered during the course of this study. Therefore, Katayama
13 fails to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising
14 LDL-C.

15 16. Kelley²⁸⁰

16 In Kelley, 34 men with an average triglyceride level of 226 mg/dL participated in a
17 double-blind, randomized, placebo-controlled parallel study. The DHA group received 7.5 g/day
18 of DHA oil containing 3 g of DHA, and the placebo group received olive oil. Fasting lipid
19 profiles were measured at the beginning of the study and after 90 days. Kelley did not
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21 ²⁷⁸ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS*
Analysis of PGI₂ and PGI₃ Levels, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

22 ²⁷⁹ *Id.* at 3.

23 ²⁸⁰ Kelley et al., *Docosahexaenoic acid supplementation improves fasting and postprandial lipid profiles in*
hypertriglyceridemic men, 86 AM. J. CLIN. NUTR. 324-33 (2007).

1 administer or study the effects of EPA. Kelly was considered by the USPTO during prosecution
2 of the patents at issue.

3 Defendants contend that Kelley demonstrates that it was known in the art that EPA and
4 DHA have different effects on lipid metabolism.²⁸¹ Defendants contend that Kelley shows that it
5 was known that DHA was responsible for the increase in LDL-C.²⁸² Defendants contend that
6 Kelley taught that an increase in LDL cholesterol is harmful.²⁸³

7 Kelley does not show that EPA and DHA have different effects on lipid metabolism or
8 that DHA is responsible for the increase in LDL-C. The study's goal was to examine the effect
9 of DHA supplementation on lipids, and as such it compared DHA's effects against placebo's.
10 This study was not designed to test whether EPA and DHA have differential effects on lipid
11 metabolism. In fact, Kelley does not administer or study the effects of EPA at all. Therefore, a
12 person of ordinary skill would not rely on Kelley to draw any conclusions related to possible
13 differences between the lipid effects of EPA and DHA.

14 In fact, Kelley suggests that the increase in LDL-C observed is a general phenomenon
15 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
16 therapy.²⁸⁴ Further, the DHA-rich oil contained other saturated and polyunsaturated fatty acids.
17 As such, a person of ordinary skill would have known that Kelley is unsuitable for evaluating the
18 independent effects of DHA because it is not clear how much of the supplement's effects can be
19 attributed to DHA.²⁸⁵

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21 ²⁸¹ Defendants' Joint Invalidity Contentions at 208.

22 ²⁸² Defendants' Joint Invalidity Contentions. at 207.

23 ²⁸³ Defendants' Joint Invalidity Contentions at 221.

24 ²⁸⁴ Kelley at 329.

²⁸⁵ See Mori 2006 at 96.

1 Kelley does not teach that the increase in LDL-C is harmful. In fact, Kelley teaches that
2 “it is unlikely this increase [in LDL-C] is detrimental because no increase was observed in the
3 overall number of LDL particles.”²⁸⁶ Kelley compares its results to a fibrate study where
4 “[d]espite a slight increase in LDL cholesterol, there was a decrease in LDL particle number,
5 which was associated with a reduction in [cardiovascular disease] events.”²⁸⁷ Kelly explains that
6 “it is the number, not the size, of LDL particles that is responsible for the greater [cardiovascular
7 disease] risk.”²⁸⁸ Kelly further states that “the lack of an increase in the concentration of total
8 LDL particles and a significant reduction in the concentrations of small LDL particles after DHA
9 supplementation should lessen any concern about a possible increase in [cardiovascular disease]
10 risk that may be inferred from the increase in LDL cholesterol.”²⁸⁹ Kelley concludes that DHA
11 supplementation may improve cardiovascular health because overall it “reduced the
12 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
13 cardioprotective lipoproteins.”²⁹⁰ Kelley demonstrates that while an increase in LDL-C was seen
14 as a *possible* adverse health effect, a person of ordinary skill in the art understood that the
15 increase in LDL-C seen with DHA, and omega-3 fatty acids generally, was most likely not
16 detrimental because DHA also decreased small, dense LDL particles and did not increase overall
17 LDL particle number. Therefore, a person of ordinary skill would not have been motivated to
18 use EPA instead of DHA or fish oil to treat hypertriglyceridemia based on Kelley.
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21 ²⁸⁶ *Id.* at 329.

22 ²⁸⁷ *Id.*

23 ²⁸⁸ *Id.*

24 ²⁸⁹ *Id.* at 330.

²⁹⁰ *Id.* at 332.

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17. Kris-Etherton²⁹¹

Kris-Etherton addressed distinctions between plant-derived and marine-derived omega-3 fatty acids. Based on evidence from studies, Kris-Etherton made recommendations reflecting the current state of knowledge regarding both fish consumption and omega-3 fatty acid supplementation. Kris-Etherton teaches that patients in need of TG lowering should consume “two to four grams of EPA+DHA per day.”²⁹² Kris-Etherton does not distinguish between EPA and DHA and in fact recommends the administration of EPA and DHA *together*. Kris-Etherton does not provide any teaching related to the administration of EPA alone.

18. Kurabayashi²⁹³

Kurabayashi studied the effects of estriol and EPA combination therapy on symptomatic menopausal Japanese women. The study randomly assigned 141 women with TG levels between 150 and 400 mg/dl to groups treated with 2 mg daily estriol²⁹⁴ (72 women) or 1.8 g daily EPA and 2 mg daily estriol (69 women).²⁹⁵ Because this study was conducted only in symptomatic menopausal Japanese women, a person of ordinary skill would not have expected the results to be applicable to the general population. Further, because EPA was administered with estriol, a person of ordinary skill in the art would not rely on these results to draw any conclusions regarding EPA’s effect alone.

²⁹¹ Kris-Etherton *et al.*, *Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease*, 23 ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY e20-e30 (2003).

²⁹² Kris-Etherton at 9.

²⁹³ Kurabayashi *et al.*, *Eicosapentaenoic Acid Effect on Hyperlipidemia in Menopausal Japanese Women*, 96 OBSTET. GYNECOL. 521-528 (2000).

²⁹⁴ Estriol is a form of estrogen.

²⁹⁵ Kurabayashi at 521.

1 This study measured different blood-lipid parameters of the subjects at 12, 24 and 48
2 weeks. The study found no significant impact on LDL-C and Apo-B levels as compared to
3 control at each of these three time points.²⁹⁶ In addition, the study reported the level of change in
4 LDL-C and Apo-B following 48 weeks of therapy, but those results were not control-adjusted.
5 The “most important finding” of this study was that combination therapy with EPA and estriol
6 significantly decreased serum TG compared with estriol alone.²⁹⁷

7 19. Leigh-Firbank²⁹⁸

8 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
9 responsible for the increase in LDL-C levels.”²⁹⁹ However, Leigh-Firbank administered fish oil,
10 which provided 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with
11 triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the
12 effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA
13 alone. This reference not only fails to administer the claimed therapeutic dose of 4g/day EPA, it
14 also fails to meet the EPA purity limitation by administering fish oil which contained almost
15 equal amounts of both EPA and DHA. Further, the fish oil was administered for only six weeks
16 to patients with baseline triglyceride levels < 500 mg/dL.

17 Although Leigh-Firbank repeatedly admits that studies examining EPA and DHA’s
18 impact on lipid metabolism have produced conflicting results, it attempts to make conclusions
19 regarding the effect of EPA and DHA alone, based on associations between platelet DHA and
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21 ²⁹⁶ Kurabayashi at 524–525.

22 ²⁹⁷ Kurabayashi at 525.

23 ²⁹⁸ Leigh-Firbank *et al.*, *Eicosapentaenoic acid and docosahexaenoic acid from fish oils: differential associations*
with lipid responses, 87 BR. J. NUTR. 435, 442 (2002).

24 ²⁹⁹ Defendants’ Joint Invalidation Contentions at 206.

1 EPA and changes in lipid parameters such as triglycerides and LDL-C after administering fish
2 oil.³⁰⁰ In fact, the last sentence of the Leigh-Firbank publication states that “further work is
3 needed in order to elucidate the mechanisms by which DHA and EPA impact on lipid
4 metabolism at the hepatic and systemic level.” Leigh-Firbank cannot comment on the effect of
5 EPA and DHA alone because it did not administer EPA and DHA separately. Therefore, a
6 person of ordinary skill would have known that the fish oil administered by Leigh-Firbank is not
7 indicative or predictive of the impact of the EPA or DHA alone on lipid parameters.³⁰¹

8 In addition, one of Leigh-Firbank’s “findings” was that changes in platelet phospholipid
9 EPA were independently associated with the decrease in fasting triglycerides.³⁰² This “finding”
10 has been refuted by many studies before and after Leigh-Firbank, which demonstrate that both
11 EPA and DHA have a hypotriglyceridemic effect.³⁰³ It is widely accepted that DHA has a
12 hypotriglyceridemic effect. This error leads one of ordinary skill in the art to question the
13 validity of the study method used in this article and its results.

14 Therefore, Leigh-Firbank’s administration of fish oil containing both EPA and DHA, and
15 their “findings” that DHA was not associated with a decrease in triglycerides makes the
16 publication’s statements related to independent effects of EPA and DHA unreliable. Therefore,
17 Leigh-Firbank fails to substantiate Defendants’ assertion that it was known that DHA, and not
18 EPA, was responsible for increasing LDL-C.

21 ³⁰⁰ See, e.g., Leigh-Firbank at 436, 442 and 443.

22 ³⁰¹ See Mori 2006 at 96.

23 ³⁰² Leigh-Firbank at 440.

24 ³⁰³ Grimsgaard at 654

1 **20. Lovaza PDR**³⁰⁴

2 Lovaza is a lipid regulating agent which contains approximately 465 mg of EPA ethyl
3 ester and 375 mg of DHA ethyl ester. Lovaza is indicated as “an adjunct to diet to reduce
4 triglyceride (TG) levels in adult patients with very high (\geq 500 mg/dL) triglyceride levels.”³⁰⁵
5 The Lovaza PDR teaches that “Lovaza 4g per day reduced median TG, VLDL-C, and non-HDL-
6 C levels and increased median HDL-C from baseline relative to placebo. Lovaza treatment to
7 reduce very high TG levels may result in elevations in LDL-C and non-HDL-C in some
8 individuals. Patients should be monitored to ensure that the LDL-C level does not increase
9 excessively.”³⁰⁶

10 Defendants point to the Omacor and Lovaza labels as evidence that a person of ordinary
11 skill in the art would understand that “the use of the word ‘hypertriglyceridemia’ in WO ‘118
12 was meant to include the hypertriglyceridemia of patients being treated with Omacor/Lovaza, *i.e.*
13 with triglyceride levels greater than or equal to 500 mg/dL.”³⁰⁷ To the contrary, the Omacor and
14 Lovaza labels provide evidence that the very high TG patient population is considered separate
15 and distinct from patients with lower TG levels. When approving Lovaza, the FDA recognized
16 the important differences between very-high TG patients and the lower TG classifications, and
17 only granted pharmaceutical treatment indications for the very-high TG populations and not
18 borderline-high or high TG groups.

19 The Lovaza PDR teaches that the administration of 465 mg of EPA ethyl ester and 375
20 mg of DHA ethyl ester, to patients with very high TG levels, will lower TGs but also raise LDL-

21 _____
22 ³⁰⁴ Lovaza®, Physicians’ Desk Reference 2699 (62d ed. 2007) (“Lovaza PDR”)

23 ³⁰⁵ Lovaza PDR at 2700.

24 ³⁰⁶ *Id.*

³⁰⁷ Defendants’ Joint Invalidation Contentions at 46.

1 C. The Lovaza PDR does not disclose a method to effectively reduce TG levels without
2 substantially increasing LDL-C. Indeed, the Lovaza PDR teaches the exact opposite, that the
3 EPA/DHA composition contained within the reference would cause a significant increase in
4 LDL-C levels in the very high TG patient population, for whom the product is indicated. The
5 Lovaza PDR further does not differentiate between EPA and DHA.

6 **21. Lovegrove³⁰⁸**

7 Lovegrove investigated whether the British Indo-Asian Sikh population had higher TG
8 levels than Europeans, and whether moderate dietary fish-oil intake could reverse that
9 difference.³⁰⁹ Lovegrove administered 4g fish oil (providing 367 mg EPA and 225 mg DHA) or
10 4g olive oil to 44 Europeans and 40 Indo-Asian Sikhs for 12 weeks. The European group had a
11 baseline TG level of approximately 106 mg/dl and the Indo-Asian Sikh group had a baseline TG
12 level of approximately 150 mg/dl. The results of this therapy yielded no so significant change in
13 LDL-C levels or in Apo-B levels.³¹⁰

14 This study was designed to explore the specific diet and mechanisms involved in the
15 increased mortality from coronary artery disease in a specific subgroup of the people, British
16 Indo-Asians. A person of ordinary skill would not have expected the results to be applicable to
17 the general population. Further, the study administered a mixture of EPA and DHA, therefore a
18 person of ordinary skill would not be able to draw any conclusions related to the effect of EPA or
19 DHA alone.

21 ³⁰⁸ Lovegrove, *et al.*, *Moderate fish-oil supplementation reverses low-platelet, long-chain n-3 polyunsaturated fatty*
22 *acid status and reduces plasma triacylglycerol concentrations in British Indo-Asians*, 79 AM. J. CLIN. NUTR. 974-
982 (2004).

23 ³⁰⁹ Lovegrove at 974.

24 ³¹⁰ Lovegrove at 978, table 2.

1 **22. Maki**³¹¹

2 Defendants rely on Maki to demonstrate that a POSITA would have recognized that
3 DHA, and not EPA, was responsible for raising bad cholesterol.³¹² Maki was considered by the
4 USPTO during prosecution of the patents at issue.

5 However, Maki was designed to assess the impact of 1.52g/day of DHA supplements on
6 the serum lipid profile of patients with below-average levels of HDL-C levels. Maki does not
7 test EPA; therefore one cannot draw any conclusion related to EPA from this study. Contrary to
8 Defendants’ assertion, Maki does not disclose that DHA was responsible for the increase in
9 LDL-C levels.³¹³ Maki merely demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic
10 acid was administered to patients with borderline-high TG levels, an increase in LDL-C was
11 observed. However, one cannot attribute the rise in LDL-C solely to DHA, because the authors
12 admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have also
13 contributed to the elevation in LDL cholesterol.”³¹⁴ Further, Maki suggests that the increase in
14 LDL-C *is* benign, because “the lack of increase in the total/HDL cholesterol ratio, the decline in
15 the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried
16 by small, dense LDL particles render the changes in LDL cholesterol level less worrisome.”³¹⁵

17 While the results of Maki does show an increase in LDL-C, it is attributed to both DHA
18 and palmitate, and they specifically state that the increase in LDL-C is “less worrisome” because
19

20 ³¹¹ Maki *et al.*, *Lipid responses to a dietary docosahexaenoic acid supplement in men and women with below*
21 *average levels of high density lipoprotein cholesterol*, 24 J. AM. COL. NUTR. 189-99 (2005).

21 ³¹² Defendants’ Joint Invalidity Contentions at 194.

22 ³¹³ Defendants’ Joint Invalidity Contentions at 206.

23 ³¹⁴ Maki at 197.

24 ³¹⁵ Maki at 197.

1 of the other more beneficial effects of the capsules administered to the patients. Further, the
2 increase in LDL-C was attributable to “an increase in cholesterol carried by larger, less dense
3 particles.”³¹⁶ There was a “near significant mean reduction in cholesterol carried by small, dense
4 LDL₃ + LDL₄ particles in the DHA supplemented group . . . result[ing] in a significant net
5 reduction in the DHA supplemented group, relative to controls, in the percentage of LDL
6 cholesterol carried by small, dense particles.”³¹⁷

7 **23. Mataki³¹⁸**

8 The study included thirty patients (fifteen males and fifteen females with the mean age of
9 68.5) who had been referred to a hospital in Japan. The patients had baseline total serum
10 cholesterol level above 220 mg/dL. Sixteen patients were allocated to Group A received a
11 combination of EPA (1.8 g/day) and HMG CoA reductase inhibitors (5 mg/day of simvastatin or
12 10 mg/day of pravastatin) for the first 12 weeks and only HMG CoA reductase inhibitors for the
13 next 12 weeks. Nine patients were allocated to Group B received EPA (1.8 mg/day) alone for 12
14 weeks. Five patients were allocated to Group C received HMG CoA reductase inhibitors for 12
15 weeks. Only the data from Group A were published in Mataki.

16 Defendants contend that Mataki shows that treatment with EPA and a statin significantly
17 reduce TG levels compared to treatment with a statin alone, and that the combination may be
18 effective in treating subjects with high total cholesterol and TG.³¹⁹

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20
21 ³¹⁶ Maki at 195.

22 ³¹⁷ *Id.*

23 ³¹⁸ Mataki *et al.*, *Effect of Eicosapentaenoic Acid in Combination with HMG-CoA Reductase Inhibitor on Lipid Metabolism*, 5(1) INT.MED. J. 35-36 (1998).

24 ³¹⁹ Defendants’ Joint Invalidity Contentions at 186.

1 Mataka shows that EPA and statin in combination did not significantly reduce total
2 cholesterol, LDL-C, APO-B, or APO-E compared to statin alone.³²⁰ In fact, LDL-C and total
3 cholesterol were higher when patients were treated with EPA and statin compared to statin
4 alone.³²¹

5 Moreover, Mataka does not disclose data from treating patients with EPA only. Further,
6 there was no placebo group in the study, and it does not disclose purity of EPA or DHA content
7 in the composition. Without placebo, one cannot distinguish between the effect of the placebo
8 from that of the active agent.

9 **24. Matsuzawa³²²**

10 Defendants rely on Matsuzawa to demonstrate the “known clinical benefits of
11 administering pure EPA-lowering triglycerides without raising LDL-C.”³²³ Matsuzawa was
12 considered by the USPTO during prosecution of the patents at issue.

13 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of
14 overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation
15 of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and
16 13 were evaluated for improvement in serum triglycerides levels.³²⁴ It is unclear which of the 26
17 patients were included in each separate evaluation; therefore one cannot determine the baseline
18 lipid characteristics for each subset of patients evaluated. Further, the small sample size makes it

19 _____
20 ³²⁰ Mataka at 36.

21 ³²¹ *Id.*

22 ³²² Matsuzawa *et al.*, Effect of Long-Term Administration of Ethyl Icosapentate (MND-21) in Hyperlipidaemic
23 Patients, 7 J. CLIN. THERAPEUTIC & MEDICINES 1801-16 (1991) (Defendants’ Translation at
24 ICOSAPENT_DFNDTS00006440).

³²³ Defendants’ Joint Invalidity Contentions at 206.

³²⁴ Matsuzawa at ICOSAPENT_DFNDTS00006446 and ICOSAPENT_DFNDTS00006458.

1 less likely that the results of this study can be generalized as an effect on the population as a
2 whole. Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
3 2% decrease, but then a 1% increase in LDL-C by the end of 52 weeks.³²⁵ Matsuzawa
4 acknowledges that there have been conflicting results related to the LDL-C impact of EPA
5 preparations that lowered triglyceride levels.³²⁶ At best, Matsuzawa demonstrates the
6 uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia.
7 Matsuzawa also found no effect on Apo-B throughout the period of treatment. Further, the study
8 was not placebo controlled. Without placebo, one cannot distinguish between the effect of the
9 placebo from that of the active agent.

10 Matsuzawa does not disclose the purity of the Epadel (MND-21) used in the study. The
11 purity of Epadel® has varied over time and across different formulations of the product,
12 therefore it is difficult to determine the purity of the version of Epadel® used unless it is
13 specified by the disclosure. One cannot simply rely on the fact that Epadel® was administered
14 and assume that the composition comprised at least about 96%, by weight of all fatty acids
15 present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to
16 provide a reference disclosing the purity of the form of Epadel® used in the Matsuzawa study.
17 Nishikawa,³²⁷ published in 1997, discloses a form of Epadel® that was a 91% E-EPA
18 preparation. Nishikawa reflects that versions of Epadel® used in some clinical studies do not
19 have the requisite purity.

21 _____
22 ³²⁵ *Id.* at ICOSAPENT_DFNDTS00006450.

23 ³²⁶ *Id.* at ICOSAPENT_DFNDTS00006454.

24 ³²⁷ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS
Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

1 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
2 and one participant with TG levels > 1,000 mg/dL.³²⁸ Based on this disclosure, only one patient
3 definitively had a baseline TG level \geq 500 mg/dL. When analyzing the lipid impact of Epadel®,
4 Matsuzawa excluded the patient with the TG level > 1,000 mg/dL because he was a “heavy
5 drinker” and the “effect of alcohol made it impossible to assess triglyceride levels.”³²⁹ Fig. 4,
6 which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12
7 patients with TG > 150 mg/dL was well below 500 mg/dL.

8 Matsuzawa examined only 12 patients with TG levels > 150 mg/dL who were
9 administered only 2.7 g/day of ethyl icosapentate. The results showed a modest effect on
10 triglycerides, therefore one of ordinary skill in the art would not expect an impact on LDL-C.
11 Further, the LDL-C results are mixed, at first showing a 2% decrease, but then a 1% increase in
12 LDL-C by the end of 52 weeks for patients.³³⁰ As mentioned above, one is unable to determine
13 the baseline lipid characteristics of the 16 patients adopted for the evaluation of changes in LDL-
14 C levels. However, the disclosure makes clear that the 4 patients with serum triglyceride levels \geq
15 400 mg/dL were excluded because the Friedewald’s Equation was used to calculate LDL-C
16 levels, and the Friedewald’s Equation cannot be used for patients with triglyceride levels \geq 400
17 mg/dL.³³¹ Therefore, the LDL-C results reflect the LDL-C changes in patients with triglyceride
18 levels < 400 mg/dL.

19 Therefore, Matsuzawa discloses administration of the wrong dose of Epadel, the purity of
20 which is unknown, to the wrong patient population. The discussion related to LDL-C excludes
21

22 ³²⁸ *Id.* at ICOSAPENT_DFNDTS00006462.

23 ³²⁹ *Id.* at ICOSAPENT_DFNDTS00006449.

24 ³³⁰ *Id.* at ICOSAPENT_DFNDTS00006450 and ICOSAPENT_DFNDTS00006473-74.

³³¹ *Id.* at ICOSAPENT_DFNDTS00006450.

1 patients with triglyceride levels \geq 400 mg/dL, and the small sample size makes it less likely that
2 the results of this study can be generalized as an effect on the population as a whole. Therefore,
3 Matsuzawa fails to substantiate Defendants’ assertion that pure EPA lowers triglycerides without
4 raising LDL-C.

5 **25. Mori 2000³³²**

6 Defendants rely on Mori 2000 to demonstrate “the knowledge that DHA was responsible
7 for the increase in LDL-C levels.”³³³ Defendants assert that, in light of this knowledge, a person
8 of ordinary skill in the art would have been “motivated to replace the mixed fish oil active
9 ingredient in Lovaza with pure EPA.”³³⁴ Mori 2000 was considered by the USPTO during
10 prosecution of the patents at issue.

11 As Defendants acknowledge, Mori 2000 discloses a trial involving “*mildly*
12 *hyperlipidemic men.*” Specifically, the mean baseline triacylglycerol concentration was 2.01
13 mmol/L (178 mg/dL) for the patients who were administered EPA, and 2.25 mmol/L (199
14 mg/dL) for the patients who were administered DHA.³³⁵ These levels are significantly lower
15 than the TG concentration of patients targeted by the claimed methods (at least 500 mg/dL) and
16 more than 3-fold lower than the median TG in the MARINE trial (680 mg/dL).

17 Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it
18 also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention.

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20 _____
21 ³³² Mori *et al.*, *Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and*
lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men, 71 AM. J. CLIN. NUTRI. 1085
(2000) (“Mori 2000”).

22 ³³³ Defendants’ Joint Invalidity Contentions at 206.

23 ³³⁴ *Id.*

24 ³³⁵ Mori 2000 at 1088.

1 | Mori 2000 concludes that the changes effected by DHA supplementation “may represent a more
2 | favorable lipid profile than after EPA supplementation.”³³⁶ For example, it states that “DHA, but
3 | not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a
4 | significant increase in the HDL₂-cholesterol subfraction, without adverse effects on fasting
5 | glucose concentrations.”³³⁷ Mori 2000 also states that “[d]espite an increase in LDL cholesterol
6 | after DHA supplementation, LDL particle size increased—a finding that may be favorable.”³³⁸
7 | Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori 2000, a person of
8 | ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of
9 | what Defendants argue in their contentions.

10 | Defendants rely on hindsight bias to argue that a person of ordinary skill would have
11 | been motivated to use purified EPA, since Mori 2000 teaches that DHA may provide a more
12 | favorable lipid profile than EPA. A person of ordinary skill would take into consideration the
13 | entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
14 | Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
15 | would consider.

16 | **26. Mori 2006³³⁹**

17 | Mori 2006 surveys literature comparing the effects of EPA and DHA on cardiovascular
18 | health. Mori 2006 was considered by the USPTO during prosecution of the patents at issue.

21 | ³³⁶ Mori 2000 at 1092.

22 | ³³⁷ Mori 2000 at 1088.

23 | ³³⁸ Mori 2000 at 1092.

24 | ³³⁹ Mori *et al.*, *The Independent Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Cardiovascular Risk Factors in Humans*, 9 CURRENT OPINION CLINICAL NUTRITION & METABOLIC CARE 95, 98 (2006).

1 Defendants assert that Mori 2006 summarized these publications as showing that “EPA
2 reduced total cholesterol and LDL-C, while DHA generally did not.” In particular, Defendants
3 quote Mori 2006 as providing that “[t]he favourable effects of fish oils were primarily attributed
4 to eicosapentaenoic acid (EPA), despite the fact that some fish provide substantial quantities of
5 decosahexaenoic acid (DHA).”³⁴⁰ However, Defendants purposefully omit the discussion later
6 in the same paragraph, where the authors refute this statement, stating that more recent data “*now*
7 demonstrate that DHA, like EPA, has important haemodynamic and anti-atherogenic
8 properties.”³⁴¹ Defendants conveniently leave out the full disclosure in an attempt to
9 misconstrue Mori 2006’s teachings.

10 Mori 2006 also places importance on the results from controlled studies as opposed to
11 uncontrolled studies. Without placebo, one cannot distinguish between the effect of the placebo
12 from that of the active agent. Moreover, contrary to Defendants’ assertion, Mori 2006 does not
13 demonstrate that DHA is responsible for increases in LDL-C or that EPA supplementation
14 reduces LDL-C.³⁴² For controlled studies, Mori 2006 found that for studies administering
15 purified DHA, “LDL cholesterol was unchanged in all but one study,” and “EPA
16 supplementation has had little effect on . . . LDL cholesterol”.³⁴³ Decreases in LDL-C after EPA
17 administration was observed only in uncontrolled studies, which Mori 2006 places less
18 importance on. More significantly, none of the studies surveyed by Mori 2006 involved patients
19 with TG levels ≥ 500 mg/dL, and all but one controlled study were for durations less than 12
20 weeks. Therefore, based on data collected and reviewed by Mori 2006, a person of ordinary skill

21
22 ³⁴⁰ Defendants’ Joint Invalidity Contentions at 116.

23 ³⁴¹ Mori 2006 at 95-96.

24 ³⁴² Defendants’ Joint Invalidity Contentions at 115.

³⁴³ Mori 2006 at 98.

1 in the art would not have had a reasonable expectation that pure EPA would reduce LDL-C when
2 administered to patients with TG levels \geq 500 mg/dL for 12 weeks.

3 Mori 2006 also shows that “both EPA and DHA reduce blood triglycerides.”³⁴⁴ It states
4 that “DHA supplementation reduced triglycerides in most controlled studies by approximately
5 17-33%.”³⁴⁵ Mori 2006 further discloses that EPA reduced triglycerides in the surveyed studies,
6 but the reduction, ranging from 12% to 23% in controlled studies, was no greater than with DHA
7 supplementation.³⁴⁶ Therefore, a person of ordinary skill would not have been motivated to use
8 purified EPA over DHA or Lovaza for reducing triglycerides.

9 Ultimately, based on its review of publications comparing the effects of EPA and DHA
10 on cardiovascular health, Mori 2006 concludes that, “[b]oth [EPA and DHA] are equally
11 effective in reducing serum triglycerides, but DHA and not EPA increased HDL cholesterol and,
12 in particular, the HDL₂ cholesterol sub-fraction.”³⁴⁷ Furthermore, Mori 2006 discloses DHA’s
13 other beneficial effects on cardiovascular health. For example, Mori 2006 states that “DHA may
14 be more favourable in lowering blood pressure and improving vascular function, raising HDL
15 cholesterol and attenuating platelet function.”³⁴⁸ Based on the antiatherogenic and other
16 cardiovascular benefits of DHA disclosed by Mori 2006, a person of ordinary skill would not
17 have been motivated to use purified EPA over DHA or Lovaza. Again, Defendants rely on
18 hindsight bias to argue that a person of ordinary skill would have been motivated to use purified
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21 ³⁴⁴ *Id.*

22 ³⁴⁵ *Id.*

23 ³⁴⁶ *Id.*

24 ³⁴⁷ *Id.* at 101.

³⁴⁸ *Id.* at 101-102.

1 EPA, since Mori 2006 teaches that both EPA and DHA are equally effective in reducing TG, but
2 DHA, and not EPA, beneficially increased HDL-C and LDL particle size.³⁴⁹

3 **27. Nakamura³⁵⁰**

4 In Nakamura, either 900 mg/day or 1.8 g/day of EPA was administered in combination
5 with statin for 30 months to 1 male and 13 female subjects who were already on statin therapy.
6 Nakamura was considered by the USPTO during prosecution of the patents at issue.

7 Defendants contend that Nakamura taught administration of >90% pure EPA-E to at least
8 one patient with triglyceride level of 558 mg/dL.³⁵¹ Defendants contend that Nakamura shows
9 combination of EPA and statin may be more effective than statin alone.³⁵²

10 The mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the
11 baseline TG values for the other patients was well below 500 mg/dL.³⁵³ The EPA that was
12 administered had only 90% purity, and it is unclear how much DHA was contained in the
13 composition. Moreover, there was no placebo control in the study. Without placebo, one
14 cannot distinguish between the effect of the placebo from that of the active agent.

15 Nakamura shows that a person of ordinary skill did not differentiate EPA from fish oil
16 when discussing its lipid effects. Nakamura says that “fish oil can lower plasma lipid levels.”³⁵⁴

17
18
19 ³⁴⁹ *Id. at 98.*

20 ³⁵⁰ Nakamura *et al.*, *Joint Effects of HMG-CoA Reductase Inhibitors and Eicosapentaenoic Acids on Serum Lipid
Profile and Plasma Fatty Acid Concentrations in Patients with Hyperlipidemia*, 29 INT. J. CLIN. LAB. RES. 22-25
(1999).

21 ³⁵¹ Defendants’ Joint Invalidity Contentions at 217.

22 ³⁵² Defendants’ Joint Invalidity Contentions at 118-19.

23 ³⁵³ Nakamura at 23, Tables 1 and 2.

24 ³⁵⁴ Nakamura at 22.

1 It also states that “fish oil . . . safely reduced both serum TC and TG concentrations.”³⁵⁵
2 Nakamura’s data demonstrated only that “the combination therapy of HMG-CoA reductase
3 inhibitors plus EPA-E significantly decreased serum TC and TG concentrations in patients
4 hyperlipidemia more than HMG-CoA reductase inhibitor therapy alone.”³⁵⁶ Notably, Nakamura
5 does not disclose any data related to EPA’s effect on LDL-C. Nakamura does not make any
6 conclusions about EPA therapy alone, compared to combination therapy of HMG-CoA reductase
7 plus EPA.

8 **28. Nelson³⁵⁷**

9 Nelson investigated the effects of a high DHA-diet on several lipid parameters. Subjects
10 were fed either a high DHA diet containing 6g per day of DHA, or a low-DHA diet (control) that
11 contained less than 50 mg of DHA for 90 days. The study found that there was a statistically
12 significant decrease in TG levels and a statistically significant increase in HDL-C levels for the
13 high DHA diet group.³⁵⁸ The study found that “[t]he addition of 6 g/d of DHA to a natural-food
14 diet for 90 days did not affect the total plasma cholesterol value or the LDL-cholesterol (C)
15 value.”³⁵⁹

20 ³⁵⁵ *Id.* at 24.

21 ³⁵⁶ *Id.*

22 ³⁵⁷ Nelson et al., *The Effect of Dietary Docosahexaenoic Acid on Plasma Lipoproteins and Tissue Fatty Acid Composition in Humans*, 32 LIPIDS 1137-46 (1997).

23 ³⁵⁸ Nelson at 1139.

24 ³⁵⁹ *Id.*

1 **29. Nestel**³⁶⁰

2 Nestel tested whether EPA and DHA improve systemic arterial compliance in
3 dyslipidemic subjects. Subjects were randomly assigned to receive 3g EPA per day, 3g DHA per
4 day or a placebo in a 7 week parallel, double-blind trial. The results of the study found that
5 “[p]lasma total cholesterol and LDL cholesterol did not change significantly over time with
6 either treatment or placebo.”³⁶¹ Plasma total triacylglycerol and VLDL triacylglycerol
7 concentrations fell significantly for both of the n-3 fatty acid groups, and the reductions in
8 triacylglycerol values were not significantly different between the EPA and DHA groups.³⁶²
9 HDL-C rose in all three groups, but the increase did not differ among the groups.³⁶³

10 Defendants contend that Nestel demonstrates that products containing DHA were
11 reported to increase LDL-C levels while products containing EPA did not.³⁶⁴ Defendants
12 contend that, based on Nestel, one of ordinary skill in the art would have a reasonable
13 expectation that a composition comprising EPA, but not DHA, would lower non-HDL-C
14 levels.³⁶⁵ Defendants’ characterization of Nestel does not accurately reflect the data presented.

15 Nestel reported non-significant effects on total cholesterol and LDL-C. Nestel clearly
16 states that “LDL cholesterol did not change significantly over time with either treatment or
17 placebo.” Defendants attempt to interpret *non-significant effects* of DHA and EPA as evidence
18 that it was known that DHA increases LDL-C while EPA does not, even though the authors
19

20 ³⁶⁰ Nestel et al., *The n-3 Fatty Acids Eicosapentaenoic acid and Docosahexaenoic Acid Increase Systemic Arterial Compliance in Human*, 76 AM. J. CLIN. NUTR. 326-30 (2002).

21 ³⁶¹ Nestel at 328.

22 ³⁶² *Id.*

23 ³⁶³ *Id.*

24 ³⁶⁴ Defendants’ Joint Invalidation Contentions at 215-16.

³⁶⁵ Defendants’ Joint Invalidation Contentions at 229.

1 specifically state that neither EPA nor DHA had a significant effect on LDL-C. Further, Nestel
2 reports that HDL-C increased for DHA, EPA, *and* placebo but the difference between the three
3 groups was not statistically significant. Nestel does not attempt to differentiate EPA and DHA
4 on the basis of non-HDL-C or LDL-C effect.

5 **30. Nozaki³⁶⁶**

6 In Nozaki, 2.7 g/day of 90% EPA (DHA < 1%) was administered to 14 primary
7 hypercholesterolemia subjects. Nozaki was considered by the USPTO during prosecution of the
8 patents at issue.

9 Defendants contend that Nozaki shows that EPA itself reduced LDL levels and the
10 reduction in LDL-C was associated with the reduction in Apo-B. Defendants contend that
11 Nozaki suggests “that EPA and DHA have different properties against lipoprotein metabolism.”

12 A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki
13 was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA.
14 Without placebo, one cannot distinguish between the effect of the placebo from that of the active
15 agent. The purity of EPA that was administered was only 90%, and daily intake was 2.7 g/day.
16 The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185
17 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would
18 not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to
19 understand the impact of EPA therapy on the very high TG patient population. Further, a person
20 of ordinary skill would understand that the baseline LDL-C level in this small patient population
21 were abnormally high and would not have relied upon these results. Nozaki acknowledges that

22 _____
23 ³⁶⁶ Nozaki *et al.*, *Effects of Purified Eicosapentaenoic Acid Ethyl Ester on Plasma Lipoproteins in Primary*
24 *Hypercholesterolemia*, 62 INT’L J. VITAMIN & NUTRITION RES. 256 (1992).

1 “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
2 levels.³⁶⁷

3 **31. Okumura³⁶⁸**

4 In Okumura, 1.8 g/day of Epadel was administered for three months to a small group of 8
5 subjects with hypertriglyceridemia, a mean baseline TG level of 274.0. Okamura also included a
6 “control” group of 7 patients who did not have hypertriglyceridemia with a mean baseline TG
7 level of 77 mg/dL. The baseline TG levels of the treatment group and “control” group were
8 significantly different from each other. Okumura was considered by the USPTO during
9 prosecution of the patents at issue.

10 Defendants contend that Okumura shows that EPA has been administered to patients with
11 TG levels greater than 500 mg/dL.³⁶⁹ Okumura, however, makes no such disclosure and, based
12 on a statistical analysis, it is highly unlikely that even one individual in Okumura had an initial
13 baseline triglyceride level above 400 mg/dL.³⁷⁰

14 Moreover, the subjects of Okumura were not randomly assigned. The treatment group
15 had TG levels above 150 mg/dL, while the “control” group had TG levels below 150 mg/dL.
16 Okumura does not disclose the purity of the EPA administered and the DHA content in the
17 composition. Okumura also shows that there was a non-significant increase in LDL-C after EPA
18 administration.

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21 ³⁶⁷ Nozaki at 256.

22 ³⁶⁸ Okumura *et al.*, *Eicosapentaenoic Acid Improves Endothelial Function in Hypertriglyceridemic Subjects Despite Increased Lipid Oxidizability*, 324 AM. J.MED. SCI. 247-53 (2002).

23 ³⁶⁹ Defendants’ Joint Invalidation Contentions at 210.

24 ³⁷⁰ May 7, 2012 Declaration of Phillip Lavin.

1 **32. Omacor PDR**³⁷¹

2 Omacor is a lipid regulating agent which contains approximately 465 mg of EPA ethyl
3 ester and 375 mg of DHA ethyl ester. Omacor is indicated as “an adjunct to diet to reduce very
4 high (≥ 500 mg/dL) triglyceride (TG) levels in adult patients.”³⁷² The Omacor PDR discloses
5 that “Omacor 4g per day reduced median TG, VLDL-C, and non-HDL-C levels and increased
6 median HDL-C from baseline relative to placebo. Omacor treatment to reduce very high TG
7 levels may result in elevations in LDL-C and non-HDL-C in some individuals. Patients should
8 be monitored to ensure that the LDL-C level does not increase excessively.”³⁷³

9 Defendants point to the Omacor and Lovaza labels as evidence that a person of ordinary
10 skill in the art would understand that “the use of the word ‘hypertriglyceridemia’ in WO ‘118
11 was meant to include the hypertriglyceridemia of patients being treated with Omacor / Lovaza,
12 *i.e.* with triglyceride levels greater than or equal to 500 mg/dL.”³⁷⁴ To the contrary, the Omacor
13 and Lovaza labels provide evidence that the very high TG patient population is considered
14 separate and distinct from patients with lower TG levels. When approving Omacor, the FDA
15 recognized the important differences between very-high TG patients and the lower TG
16 classifications, and only granted pharmaceutical treatment indications for the very-high TG
17 populations and not borderline-high or high TG groups.

18 The Omacor PDR teaches that the administration of fish oil, to patients with very
19 high TG levels, will lower TGs but also raise LDL-C. The Omacor PDR does not disclose a
20 method to effectively reduce TG levels without substantially increasing LDL-C. Indeed, the

21 _____
22 ³⁷¹ Omacor®, Physicians’ Desk Reference 2735 (60d ed. 2006) (“Omacor PDR”).

23 ³⁷² Omacor PDR at 2735.

24 ³⁷³ *Id.*

³⁷⁴ Defendants’ Joint Invalidation Contentions at 46.

1 Omacor PDR teaches the exact opposite, that the EPA/DHA composition contained within the
2 reference would cause a significant increase in LDL-C levels in the very high TG patient
3 population, for whom the product is indicated. The Omacor PDR further does not differentiate
4 between EPA and DHA.

5 **33. Park³⁷⁵**

6 Park was published in 2003. Subjects had baseline triglyceride levels less than 200
7 mg/dL. After a 4-week placebo run-in period, the subjects were given 4 g/day of either safflower
8 oil, 95% pure EPA ethyl esters, or 95% pure DHA ethyl esters for 4 weeks. Park was considered
9 by the USPTO during prosecution of the patents at issue.

10 After four weeks of taking the supplements, subjects consumed a test drink made up of
11 87 parts of light whipping cream and 13 parts of chocolate syrup. Blood was drawn at 0, 2, 3, 4,
12 5, 7, and 9 hours after consuming the test drink. TGs, Apo-B-48, and Apo-B-100 levels were
13 measured from the blood drawn, and LDL-C was estimated using the Friedewald equation.

14 Defendants contend that Park disclosed administering 4 grams of purified EPA daily³⁷⁶
15 and that EPA and DHA were thought to have different effects on lipid metabolism as compared
16 to another.³⁷⁷ Defendants also contend that “[a]t the completion of the four weeks of treatment,
17 administration with pure EPA resulted in decreased Apo-B-100 concentrations.”³⁷⁸

18 Park does not disclose administering 4 grams of purified EPA daily to treat
19 hypertriglyceridemia. The subjects of the study had baseline TG levels less than 200 mg/dL.

21 ³⁷⁵ Park & Harris, *Omega-3 Fatty Acid Supplementation Accelerates Chylomicron Triglyceride Clearance*, 44 J.
LIPID RES. 455-463 (2003).

22 ³⁷⁶ Defendants’ Joint Invalidity Contentions at 197.

23 ³⁷⁷ *Id.* at 208.

24 ³⁷⁸ *Id.* at 128.

1 Park states that there was “no significant effect of treatment on fasting plasma TG, and total,
2 HDL, LDL, and VLDL-C concentration.”³⁷⁹

3 Park also measured lipid parameters after consuming the test drink. A person of ordinary
4 skill in the art would not have expected that lipid measurements after consuming light whipping
5 cream and chocolate syrup in healthy or borderline-high TG subjects with baseline TG levels less
6 than 200 mg/dL to predict changes in fasting lipid measurements in patients with triglycerides
7 above 500 mg/dL.

8 Park does not show that EPA and DHA had different effects on lipid metabolism as
9 compared to another. Park states that, taken together, data from prior studies suggest that “the
10 effects of EPA and DHA on plasma TG concentrations were not markedly different.”³⁸⁰ Park
11 also suggests that there might be a “synergetic effect on reducing TG concentration” when EPA
12 and DHA are taken in combination.³⁸¹ The ultimate conclusion of the study—that
13 “supplementation with EPA or DHA accelerates human chylomicron TG clearance”—further
14 demonstrates that EPA and DHA were not thought to have differential effects on lipid
15 metabolism.³⁸²

16 Park does not show that administration with pure EPA resulted in decreased Apo-B (also
17 referred to as Apo-B-100) levels at the completion of the four weeks of treatment. After four
18 weeks of treatment, the 0 hour measurement demonstrates that there was no significant
19 difference in fasting Apo-B between EPA and placebo groups.³⁸³

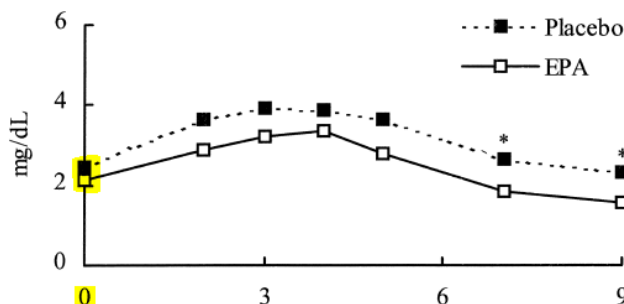
21 ³⁷⁹ Park at 457.

22 ³⁸⁰ Park at 461.

23 ³⁸¹ *Id.*

24 ³⁸² *See id.* at 462.

³⁸³ Park at 459, Fig. 4.



Moreover, Park does not show that EPA decreases LDL-C or that DHA is the fish oil component responsible for increase in LDL-C. Both EPA and DHA groups showed 5 mg/dL increase in LDL-C after 4 weeks of treatment compared to the 4-week run-in period taking olive oil.³⁸⁴ Therefore, a person of ordinary skill in the art, based on Park, would not have expected that EPA treatment would lower triglycerides without increasing LDL-C.

Furthermore, Park does not disclose all of the limitations of the claimed invention. For example, purity of EPA that was administered in Park was only 95%, and it was administered for only 4 weeks.

34. Rambjør³⁸⁵

In Rambjør, subjects with normal TG levels were separated into groups, where one group received EPA (3 g/day) and olive oil, a second group received DHA (3 g/day) and olive oil, a third group received fish oil (5 g/day), and a fourth group received a placebo of olive oil. Rambjør was considered by the USPTO during prosecution of the patents at issue.

³⁸⁴ Park at 457, Table 2.

³⁸⁵ Rambjør et al., *Eicosapentaenoic Acid Is Primarily Responsible for Hypotriglyceridemic Effect of Fish Oil in Humans*, 31 LIPIDS S-45- S-49 (1996).

1 Defendants contend that Rambjor shows that EPA and DHA have different effects on
2 lipid metabolism.³⁸⁶

3 Rambjor shows that both EPA and fish oil caused a significant increase in LDL-C. On
4 the other hand, DHA effected only a non-significant increase in LDL-C. Rambjor also disclosed
5 that fish oil decreased TG levels more than EPA. The DHA group also resulted in a decrease in
6 TG levels, but the decrease was not significant because there were not enough subjects in the
7 DHA group.

8 Furthermore, Rambjor states that, “[i]n most studies in normolipidemic subjects, n-3 FA
9 have had no significant impact on LDL C levels, but, in hypertriglyceridemic patients, LDL
10 usually increases with fish oil feeding.”³⁸⁷

11 35. Saito³⁸⁸

12 Saito was published in 1998. In the study, 1.8 g/day of Epadel (MDN-21) was
13 administered to subjects initially, but the dose was increased to 2.7 g/day if subjects exhibited
14 triglyceride abnormalities. The administration period was 12 weeks. Saito was considered by
15 the USPTO during prosecution of the patents at issue.

16 The subjects of Saito consisted of 14 males and 19 females with the average age of 57.8
17 years. Of the 33 subjects, triglyceride levels of 12 subjects were measured. The average
18 baseline triglyceride level was 294.7 mg/dL. Triglycerides were measured in four-week
19 intervals, and LDL-C levels of the subjects was estimated using the Friedewald equation.

21 ³⁸⁶ Defendants’ Joint Invalidity Contentions at 208.

22 ³⁸⁷ Rambjor at 47.

23 ³⁸⁸ Saito et al., *Results of Clinical Usage of Improved Formulation (MND-21S) Epadel Capsule 300 with Respect to*
24 *Hyperlipidemia*, 26(12) JPN. PHARMACOL. THER. 2047-62 (1998) (translation provided by Defendants at
ICOSAPENT_DFNDTS00006791).

1 Defendants contend that Saito discloses administration of highly purified EPA capsules
2 for at least 12 weeks in order to achieve the known triglyceride-lowering effects of highly
3 purified EPA.³⁸⁹ Defendants contend that Saito teaches that higher doses of highly purified EPA
4 reduce triglyceride levels to a greater extent than lower doses.³⁹⁰ Defendants contend that Saito
5 reports that treatment with EPA reduced LDL-C levels relative to baseline in subjects who were
6 not taking any additional lipid-altering therapy.³⁹¹

7 A person of ordinary skill in the art would not have concluded based on Saito that EPA
8 reduces LDL-C levels relative to baseline. The 3.2% decrease in LDL-C cited by Defendants is
9 an average of measurements made after 4, 8, and 12 weeks.³⁹² 4-week and 8-week
10 measurements are irrelevant because they are shorter than the 12-week limitation of the claimed
11 invention. Looking solely at the measurements made after 12 weeks, LDL-C actually increased
12 by 3.3%.³⁹³ Indeed, Saito states that in past studies, LDL-C levels of patients with normal
13 baseline LDL-C levels increased after administering EPA.³⁹⁴

14 Moreover, a person of ordinary skill in the art would not have concluded that the results
15 of Saito would be the same in patients with triglycerides above 500 mg/dL. There were 2
16 patients who had baseline TGs above 400 mg/dL, but both them were excluded from LDL-C data
17 reported because the Friedewald Equation cannot be applied when triglycerides are above 400
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20 ³⁸⁹Defendants' Joint Invalidity Contentions at 218.

21 ³⁹⁰ Defendants' Joint Invalidity Contentions at 218.

22 ³⁹¹ Defendants' Joint Invalidity Contentions at 219.

23 ³⁹² Saito at 18.

24 ³⁹³ *Id.*

³⁹⁴ *Id.* at 30.

1 mg/dL.³⁹⁵ As such, Saito does not disclose any information regarding the LDL-C levels of
2 subjects with TG levels above 500 mg/dL.

3 A person of ordinary skill in the art would not have concluded based on Saito that higher
4 doses of highly purified EPA reduce triglyceride level to a greater extent than lower doses. Of
5 the 12 subjects whose TG levels were measured at the beginning of the study, 7 subjects were
6 given 1.8 g/day of MND-21, and the other 5 were given 2.7 g/day of MND-21.³⁹⁶ A person of
7 ordinary skill in the art would have known that 12 subjects are a small sample size to begin with,
8 and that dividing them into two groups would make the study even weaker. Indeed, the data
9 shows that the decrease in TG levels was not statistically significant for either group.³⁹⁷ In
10 addition, the TG levels of two of the twelve subjects were not even measured after 12 weeks of
11 administration.³⁹⁸ A person of ordinary skill in the art would have found the study method of
12 Saito highly unreliable and would have concluded that it was improper to combine the results
13 from the group that received 2.7 g/day with the group that received 1.8 g/day of MND-21.

14 A person of ordinary skill in the art would have further questioned the reliability of Saito
15 because the study did not include a placebo control and was conducted exclusively in Japanese
16 patients. Without placebo, one cannot distinguish between the effect of the placebo from that of
17 the active agent. As such, a person of ordinary skill in the art would not have expected that the
18 results would be applicable to the general population.

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22 ³⁹⁵ *Id.* at 7.

23 ³⁹⁶ *Id.* at 16.

24 ³⁹⁷ *Id.*

³⁹⁸ *Id.* at 18.

1 Furthermore, Saito does not disclose all of the limitations of the claimed invention. For
2 example, the purity of EPA in the Epadel that was administered in Saito is unknown and, it is
3 unclear how much DHA was administered.

4 **36. Sanders³⁹⁹**

5 In Sanders, 21 hypertriglyceridemic men took part in the trial. One group received 15 g
6 of MaxEPA (2.7 g EPA and 1.9 g DHA), and the other group received fish oil. Sanders was
7 considered by the USPTO during prosecution of the patents at issue.

8 Defendants contend that Sanders shows that EPA lowers TG while reducing Apo-B.⁴⁰⁰

9 MaxEPA is a fish oil that contains a mixture of EPA and DHA. As such, Sanders does
10 not show that EPA lowers TG while reducing Apo-B. Moreover, the administration period was
11 only 4 weeks, and it does not disclose any data on LDL-C.

12 **37. Satoh⁴⁰¹**

13 In Satoh, 1.8 g/day of 98% pure EPA was administered for 12 weeks in patients with
14 normal to borderline high TG levels. Satoh was considered by the USPTO during prosecution of
15 the patents at issue.

16 Defendants rely on Satoh to show that pure EPA had known clinical benefit of lowering
17 triglyceride without raising LDL-C.

18 The significant decrease in LDL-C was only observed against the baseline, which is less
19 reliable than the comparison against a control group. In fact, Satoh showed that EPA had “no

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21 ³⁹⁹ Sanders *et al.*, *Influence of an algal triacylglycerol containing docosahexaenoic acid (22:6n-3) and*
docosapentaenoic acid (22:5n-6) on cardiovascular risk factors in healthy men and women, 95 BR. J. NUTR. 525-
531 (2006).

22 ⁴⁰⁰ Defendants’ Joint Invalidity Contentions at 137.

23 ⁴⁰¹ Satoh *et al.*, *Purified Eicosapentaenoic Acid Reduces Small Dense LDL, Remnant Lipoprotein Particles, and C-*
Reactive Protein in Metabolic Syndrome, 30 DIABETES CARE 144, 145 (2007).

1 significant overall effects” on LDL-C compared to the control group, as the LDL-C decreased in
2 the control group as well. Satoh indicates that “EPA may exert cardioprotective effects not by
3 changing the quantity but by improving the quality of LDL cholesterol,”⁴⁰² but that statement
4 does not indicate the impact of EPA relative to DHA, omega-3 fatty acids in general or to other
5 lipid therapies.

6 **38. Shinozaki⁴⁰³**

7 In Shinozaki, 1.8 g/day of 100% pure EPA was administered for 6-24 months to 24
8 subjects. Of these 24 subjects, 12 had elevated triglyceride levels, 10 had elevated LDL level,
9 and 9 had elevated total cholesterol levels. For the 12 patients that had elevated triglyceride
10 levels, the average baseline TG level was 240 mg/dL. Shinozaki was considered by the USPTO
11 during prosecution of the patents at issue.

12 Defendants rely on Shinozaki to show that pure EPA had known clinical benefit of
13 lowering TG levels without raising LDL-C.

14 Shinozaki says nothing about an LDL-C effect because it measured LDL particle number,
15 *not* LDL-C. Moreover, it is impossible to determine the baseline lipid characteristics of the
16 different patient groups. Patients selected for the study had one of three vascular diseases—
17 arteriosclerosis obliterans (ASO), Buerger’s disease (TAO) and abdominal aortic aneurysm
18 (AAA).

19 In Shinozaki, significant reduction in triglyceride levels did not occur until 18 months;
20 significant reduction in total cholesterol levels did not occur until 6 months; and significant
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22 ⁴⁰² *Id.* at 145.

23 ⁴⁰³ Shinozaki *et al.*, *The Long-Term Effect of Eicosapentaenoic Acid on Serum Levels of Lipoprotein (a) and Lipids*
24 *in Patients with Vascular Disease*, 2 J. ATHEROSCL. THROMB. 107-09 (1996) (translation provided by
Defendants at ICOSAPENT_DFNDTS00011751).

1 reduction in LDL particle number did not occur until 12 months. Moreover, the LDL particle
2 number decreased only in the group that had the baseline LDL particle number greater than 570
3 mg/dL.

4 Shinozaki also acknowledges that the result of its study is “compatible with the results”
5 of previous studies that administered omega-3 fatty acids: “Harris *et al.* reported that intake of n-
6 3 fatty acids produced persistent reductions in TG levels, but not in TC or LDL levels, and Gries
7 *et al.* reported that n-3 fatty acids could reduce the TG level after 6 months of treatment. The
8 effect of EPA on TG in the present study was compatible with the results of these previous
9 studies.”⁴⁰⁴ Shinozaki’s ultimate conclusion is that these findings indicate that “long term
10 administration of EPA may lower Lp(a) and serum lipids,” it does not make any conclusions
11 related to LDL-C.

12 39. Takaku⁴⁰⁵

13 Takaku was published in 1991. In the study, 2.7 g/day of Epadel (MND-21) was
14 administered to 33 patients for the average period of 42 weeks, with the target administration
15 period of 52 weeks and the minimum administration period of 24 weeks.⁴⁰⁶ The purity of the
16 Epadel used in the study was not specified. The subjects consisted of 16 males and 17 females
17 with the average age of 56.⁴⁰⁷ Of the 33 patients, 18 subjects were adopted for studying
18 improvement in serum triglyceride, and 25 subjects were adopted for studying improvement in
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20 ⁴⁰⁴ Shinozaki at 109.

21 ⁴⁰⁵ Takaku *et al.*, Study on the Efficacy and Safety of Ethyl Icosapentate (MND-21) in Treatment of Hyperlipidemia
22 Based on a Long-Term Administration Test, 7 J. CLIN. THERAPEUTICS & MEDICINE 191(1991) (translation
provided by Defendants ICOSAPENT_DFNDTS00006864).

23 ⁴⁰⁶ Takaku at ICOSAPENT_DFNDT00006875.

24 ⁴⁰⁷ *Id.*

1 total serum-cholesterol.⁴⁰⁸ Serum lipid levels, including triglyceride and LDL-C, were measured
2 at the beginning of the study and at weeks 4, 8, 12, 16, 28, 40, and 52.

3 Defendants argue that Takaku shows that EPA had known clinical benefits of lowering
4 triglycerides without raising LDL-C.⁴⁰⁹ Defendants also argue that Takaku shows that purified
5 EPA has been administered to patients with TG levels greater than 500 mg/dL.⁴¹⁰

6 A person of ordinary skill would *not* have concluded based on Takaku that EPA lowers
7 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
8 acknowledges that “only a few subjects were examined” and cautions against drawing a
9 conclusion “only from the results of the present study.”⁴¹¹ Further, the study did not include any
10 placebo control. Without placebo, one cannot distinguish between the effect of the placebo from
11 that of the active agent. In addition, the study was conducted exclusively in Japanese patients;
12 therefore a person of ordinary skill would not have expected the results to be applicable to the
13 general population. Moreover, the graph of the rate of LDL-C change in patients with normal
14 baseline LDL-C shows that the LDL-C change was volatile throughout the study period,
15 decreasing slightly at times but increasing by more than 8% at other times.⁴¹² Because of the
16 volatility in LDL-C change, a person of ordinary skill would not have been able to determine
17 what effect, if any, EPA had on LDL-C. Indeed, Takaku did not conclude that there was no
18 increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.⁴¹³

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20 ⁴⁰⁸ Takaku at ICOSAPENT_DFNDT00006874.

21 ⁴⁰⁹ Defendants’ Joint Invalidation Contentions at 206.

22 ⁴¹⁰ Defendants’ Joint Invalidation Contentions at 169.

23 ⁴¹¹ Takaku at ICOSAPENT_DFNDT00006897.

24 ⁴¹² Takaku at ICOSAPENT_DFNDT00006883, Fig. 14.

⁴¹³ Takaku at ICOSAPENT_DFNDT00006897.

1 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
2 TGs without raising LDL-C in patients with TG levels above 500 mg/dL. Only three patients
3 had baseline TG levels above 500 mg/dL.⁴¹⁴ The mean baseline TG level of the patients in the
4 study was 245 mg/dL,⁴¹⁵ and a person of ordinary skill would not have expected the results to be
5 applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from
6 the LDL-C study because measurement was not feasible due to “insufficient sample.”⁴¹⁶
7 Defendants have offered no evidence to demonstrate that the excluded patients did not include
8 those with very high TG levels. Thus it is not apparent that Takaku discloses the impact of EPA
9 therapy on LDL-C levels for even a single patient. Takaku further does not disclose the method
10 by which LDL-C levels were measured and to the extent the Friedewald equation was used, it is
11 inaccurate in patients with TG levels below 400 mg/dL. Moreover, the study does not provide
12 different LDL-C graphs based on the baseline triglyceride levels.⁴¹⁷ Therefore, it is impossible
13 to tell whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-
14 C after taking MND-21.

15 A person of ordinary skill would not have concluded based on Takaku that purified EPA
16 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
17 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
18 administration of *fish oil* to hypercholesterolemia patients.”⁴¹⁸ In contrast, Takaku states merely
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21 ⁴¹⁴ Takaku at ICOSAPENT_DFNDT00006895.

22 ⁴¹⁵ Takaku at ICOSAPENT_DFNDT00006875

23 ⁴¹⁶ Takaku at ICOSAPENT_DFNDT00006884.

24 ⁴¹⁷ Takaku ICOSAPENT_DFNDT00006882, Fig. 13.

⁴¹⁸ Takaku ICOSAPENT_DFNDT00006897.

1 that the fluctuation in LDL-C was not significant in its study.⁴¹⁹ Therefore, a person of ordinary
2 skill in the art would have concluded based on Takaku that any favorable LDL-C effect seen in
3 the study was attributable to fish oil in general, not EPA specifically.

4 Furthermore, Takaku does not disclose all of the limitations of the claimed invention.
5 For example, the purity of EPA in Epadel that was administered in Takaku is unknown and it is
6 unclear how much DHA was contained in the Epadel that was administered.

7 **40. Theobald⁴²⁰**

8 In Theobald, triacylglycerol derived from *Crypthecodinium cohnii* was administered for 3
9 months in healthy patients. Theobald reported that LDL-C levels increased by 7% when
10 compared to placebo, and a significant increase in Apo-B levels. Theobald did not report TG
11 levels.

12 Defendants contend that Theobald shows that EPA and DHA have differential effects on
13 lipid parameters. Defendants contend that Theobald taught that low doses of DHA raised LDL-
14 C levels.

15 The composition that was administered in Theobald contained significant amounts of
16 other fatty acids, including myristic acid, palmitic acid, and oleic acid.⁴²¹ Therefore, a person of
17 ordinary skill in the art would have known that the composition administered by Theobald is
18 unsuitable for evaluating the effects of DHA because it is not clear how much of the
19 supplement's effects can be attributed to DHA.⁴²² Indeed, Theobald characterizes the objective

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21 ⁴¹⁹ *Id.*

22 ⁴²⁰ Theobald *et al.*, *LDL cholesterol raising effect of low dose docosahexaenoic acid in middle-aged men and women*, 79 AM. J. CLIN. NUTR. 558-63 (2004).

23 ⁴²¹ *Id.* at 560.

24 ⁴²² *See* Mori 2006 at 96.

1 of the study as one to “determine the effect on blood lipids of a daily intake of 0.7 g DHA as
2 triacylglycerol.”⁴²³ Moreover, the amount of DHA within the composition was only 0.7g and
3 Theobald recognized that the “primary aim of the present study was to evaluate the effect of a
4 *low intake* of a triacylglycerol providing long-chain n–3 fatty acids.”⁴²⁴ A person of ordinary
5 skill would not expect the same LDL-C effect in patients with lower baseline TG levels,
6 including the healthy patients that were studied in Theobald, to occur in very-high TG patients
7 because patients with higher TG levels had different lipid responses compared to healthy
8 patients.

9 **41. Virani**⁴²⁵

10 Virani is a review paper that discusses whether Lp-PLA 2 can predict future coronary
11 events.⁴²⁶ Based on the articles examined, Virani concludes that “emerging data seem to suggest
12 that Lp-PLA2 may be proatherogenic.”⁴²⁷

13 Contrary to Defendants’ contention that Virani discloses the correlation between Lp-
14 PLA2 and Apo B levels,⁴²⁸ Virani only states that “most of the Lp-PLA2 circulates bound to
15 LDL via Apolipoprotein B.”⁴²⁹ Virani only discusses statin and fibrates, and does not mention
16 omega-3 fatty acids or fish oil.⁴³⁰ Virani shows that Lp-PLA2 was a novel biomarker and its
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18 ⁴²³ Theobald at 558 (emphasis added).

19 ⁴²⁴ *Id.* (emphasis added).

20 ⁴²⁵ Virani at 97.

21 ⁴²⁶ Virani et al., *The Role of Lipoprotein-associated Phospholipase A2 As a Marker for Atherosclerosis*, 9[2] CURR.
ATHEROSCLER. REP. 97 (2007).

22 ⁴²⁷ *Id.*

23 ⁴²⁸ Defendants’ Joint Invalidity Contentions at 230.

24 ⁴²⁹ Virani at 98.

⁴³⁰ Virani at 101-102.

1 atherogenicity was controversial at the time of invention.⁴³¹ Virani also teaches that the strength
2 of association between Lp-PLA2 levels and coronary heart disease varied.⁴³²

3 **42. Wojenski⁴³³**

4 Wojenski administered 4g/day of EPA (90%) to 9 healthy young men for 4 weeks. It was
5 not placebo controlled. Without placebo, a person of ordinary skill in the art could not
6 distinguish between the effect of the placebo from that of the active agent. The subjects of
7 Wojenski received ethyl oleate for 4 weeks, followed by no supplementation for 5 weeks,
8 received Res-Q 1000 for 4 weeks, followed by no supplementation for 4 months, and then
9 received EPA for 4 weeks. Wojenski was considered by the USPTO during prosecution of the
10 patents at issue.

11 Wojenski had no placebo control, and its small sample size makes it unlikely that its
12 results can be generalized. It involved healthy men with normal baseline triglyceride and does
13 not disclose LDL-C data. Moreover there is no evidence in Wojenski that EPA is better than
14 DHA or fish oil in reducing triglyceride.

15 **43. Woodman⁴³⁴**

16 Woodman investigated whether purified EPA and DHA have differential effects on
17 glycemic control. Subjects were randomly assigned to consume 4g EPA per day, 4g DHA per
18 day, or olive oil for 6 weeks. The results of the study showed that EPA and DHA had similar
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20 ⁴³¹ Virani at 102.

21 ⁴³² Virani at 99.

22 ⁴³³ Wojenski et al., *Eicosapentaenoic Acid Ethyl Ester as an Antithrombotic Agent: Comparison to an Extract of Fish Oil*, *BIOCHIM. BIOPHYS. ACTA.*, 1081(1):33-38 (1991).

23 ⁴³⁴ Woodman et al., *Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension*, 76 *AM. J. CLIN. NUTR.* 1007-15 (2002).

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1 impact on lipids. Administration of EPA and DHA both resulted in a statistically significant
2 decrease in TG levels, but had non-significant effects on total cholesterol, LDL-C, and HDL-
3 C.⁴³⁵

4 **44. Yokoyama 2007⁴³⁶**

5 In Yokoyama, Japanese patients were randomly assigned to receive either 1.8 g/day of
6 EPA with a statin or statin alone with a 5-year follow-up. Major coronary events were recorded
7 and lipid parameters were measured at the follow-up. Yokoyama 2007 was considered by the
8 USPTO during prosecution of the patents at issue.

9 Defendants contend that a person of ordinary skill would have been motivated to treat
10 subjects with triglycerides above 500 mg/dL with highly purified EPA because Yokoyama
11 teaches that triglyceride was reduced to a much greater extent in subjects having higher baseline
12 TG levels.⁴³⁷ Defendants also contend that Yokoyama would have given a person of ordinary
13 skill a reasonable expectation of successfully administering 4 g/day of highly-purified EPA for at
14 least 12 weeks to lower triglycerides.⁴³⁸

15 A person of ordinary skill would not have been motivated to treat subjects with TG levels
16 above 500 mg/dL with EPA based on Yokoyama. Yokoyama shows that administering EPA
17 with a statin reduces TG only slightly more than with statin alone in patients with normal to high
18 baseline TG levels.⁴³⁹ Further, Yokoyama does not compare EPA to fish oil or DHA. As such,
19 Yokoyama does not suggest that EPA would be more effective in treating patients with

20 ⁴³⁵ Woodman at 1011-1012.

21 ⁴³⁶ Yokoyama *et al.*, Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients
22 (JELIS): a Randomized Open-Label, Blinded Endpoint Analysis, 369 LANCET 1090, 1097 (2007).

23 ⁴³⁷ Defendants' Joint Invalidity Contentions at 218.

24 ⁴³⁸ Defendants' Joint Invalidity Contentions at 218.

⁴³⁹ Yokoyama 2007 at 1095, Fig. 4.

1 triglycerides above 500 mg/dL than fish oil or DHA. Therefore, a person of ordinary skill would
2 not have been motivated based on Yokoyama to treat subjects with triglycerides above 500
3 mg/dL using EPA.

4 A person of ordinary skill in the art would not have had a reasonable expectation of
5 success that administration 4 g/day of highly-purified EPA for at least 12 weeks would lower
6 triglycerides without increasing LDL-C. In Yokoyama, only 1.8 g/day of EPA was
7 administered. Moreover, Yokoyama only teaches administration of EPA with a statin, which is
8 known to reduce cholesterol levels and triglycerides. Therefore, a person of ordinary skill would
9 still have been concerned about an increase in LDL-C when administering 4 g/day of EPA
10 without a statin to patients with very high TG levels.

11 A person of ordinary skill would not have been convinced that EPA's beneficial effects
12 on coronary health could be generalized. As the study acknowledges, the population in the study
13 was exclusively Japanese, whose "average dietary intake of fish is about five times higher than
14 that in other countries."⁴⁴⁰ There was no true placebo group because the control group was
15 prescribed a statin. Moreover, Yokoyama acknowledges that it does not know "whether EPA
16 and DHA have differential effects on cardiovascular protection."⁴⁴¹

17 Moreover, a person of ordinary skill would not have been motivated to use EPA to reduce
18 triglycerides while not increasing LDL-C based on Yokoyama. The study indicated that
19 "reduction in major coronary events in the EPA groups was not related to serum LDL
20 cholesterol."⁴⁴²

22 ⁴⁴⁰ *Id.* at 1095-1096.

23 ⁴⁴¹ Yokoyama 2007 at 1096.

24 ⁴⁴² *Id.*

1 **45. Zalewski**⁴⁴³

2 Zalewski is a review paper that discusses whether Lp-PLA 2 is associated with
3 atherosclerosis. Defendants contend that Zalewski discloses that Lp-PLA2 is an enzyme that is
4 produced by inflammatory cells and co-travels in plasma with LDL, and that Lp-PLA2
5 hydrolyzes oxidized phospholipids in LDL.⁴⁴⁴

6 Zalewski only discusses statin and fibrates, and does not mention omega-3 fatty acids or
7 fish oil.⁴⁴⁵ Zalewski shows that the role of Lp-PLA2 has been controversial and it was initially
8 thought to have anti-inflammatory effects.⁴⁴⁶ Zalewski shows that the strength of association
9 between Lp-PLA2 and cardiovascular risk has varied.⁴⁴⁷ Zalewski shows that the causal link
10 between Lp-PLA2 and atherosclerosis has not been established.⁴⁴⁸

11 **V. Responses to Defendants' Joint Invalidity Contentions**⁴⁴⁹

12 Defendants, as the accused infringers, bear the ultimate burden of proving, by clear and
13 convincing evidence, that the asserted claims are invalid.⁴⁵⁰ They have failed to do so.

14 Throughout their contentions, Defendants provide a laundry list of references that
15 purportedly disclose disparate elements of a claim without identifying a specific combination of
16

17 ⁴⁴³ Andrew Zalewski & Colin Macphee, *Role of Lipoprotein-Associated Phospholipase A2 in Atherosclerosis: Biology, Epidemiology, and Possible Therapeutic Target*, 25 *ARTERIOSCLEROSIS, THROMBOSIS, & VASCULAR BIOLOGY* 923 (2005).

18 ⁴⁴⁴ Defendants' Joint Invalidity Contentions at 230.

19 ⁴⁴⁵ Zalewski at 927.

20 ⁴⁴⁶ Zalewski at 928.

21 ⁴⁴⁷ Zalewski at 926.

22 ⁴⁴⁸ Zalewski at 928.

23 ⁴⁴⁹ Plaintiffs incorporate by reference Section IV into Plaintiffs' Response to Defendants' Joint Invalidity Contentions in Section V.

24 ⁴⁵⁰ *Innovative Scuba Concepts, Inc. v. Feder Indus., Inc.*, 26 F.3d 1112, 1115 (Fed. Cir. 1994).

1 references or explaining how they can be combined, as required by the Local Rules and the law
2 of obviousness.⁴⁵¹ As such, Defendants discuss the claim elements in isolation, and fail to
3 address the claimed invention as a whole.⁴⁵² Defendants selectively cite to an isolated disclosure
4 within a reference without considering other disclosures or even the specific reference as a
5 whole. Each reference, however, must be evaluated for all that it teaches.⁴⁵³ Defendants’
6 unsupported cobbling of selective disclosures without explanation represents hindsight
7 reconstruction.⁴⁵⁴

8 Defendants fail to offer evidence that a person of skill in the art would be motivated to
9 combine those references in order to achieve the invention of the claim as a whole. Defendants
10 make conclusory statements that a particular claim element “would have been obvious” without
11 providing a reason that would have prompted a person of ordinary skill to achieve the invention
12 of the claim as a whole.⁴⁵⁵ For many claim elements, Defendants do not offer a proper obvious
13 analysis, but instead attempt to read out the claim limitation by trivializing it. Although
14

15 ⁴⁵¹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
16 *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”).

17 ⁴⁵² *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”).

18 ⁴⁵³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ⁴⁵⁴ 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”).

20 ⁴⁵⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
21 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
22 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
23 an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a
person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in
an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 convenient and expedient, Defendants’ approach does not conform with the Local Patent Rules
2 of this District, the law of claim construction, or the law of obviousness. Defendants fail to
3 establish *prima facie* obviousness with the naked assertion that it would have been obvious to
4 seek the particular claim element.

5 Similarly, Defendants fail to offer any evidence that a person of ordinary skill in the art
6 would have had a reasonable expectation of success in achieving the claimed invention. In fact,
7 other than simply identifying prior art references that purportedly disclose disparate elements,
8 Defendants fail to properly address whether a person of ordinary skill would have expected that
9 the combination to work for its intended purpose for treating the recited patient population.⁴⁵⁶
10 The mere fact that elements are capable of being physically combined does not establish
11 reasonable expectation of success.⁴⁵⁷ As such, Defendants fail to demonstrate reasonable
12 expectation of success of the claimed invention.

13 **A. The ’728 Patent**

14 **1. The ’728 Patent Claims Eligible Subject Matter Under § 101**

15 Defendants’ allegation that the asserted claims of the ’728 patent relate to ineligible
16 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
17 case under Section 101 or provide a legal or factual basis to support their allegations.

18 As an initial matter, Defendants’ disclosure is also insufficient under the Nevada Local
19 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be

20
21 ⁴⁵⁶ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
22 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
23 combined, but also that the combination would have worked for its intended purpose.”)

23 ⁴⁵⁷ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
25 combined, but also that the combination would have worked for its intended purpose.”).

1 provided.⁴⁵⁸ The bare assertion of invalidity under Section 101 without providing the grounds
2 for such an allegation and examining the elements of the asserted claims of the '728 patent does
3 not meet this requirement and thwarts the purpose of the Rules.⁴⁵⁹

4 The inquiry under Section 101 involves a two-step test: first, a court must determine
5 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
6 phenomenon, or abstract idea.⁴⁶⁰ Second, even if the claim is directed to one of these concepts, it
7 still may be patent eligible and the court must determine what else is part of the claim.⁴⁶¹

8 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
9 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
10 the '728 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
11 conventional” steps, and the only novel element related to administering the proper dosage based
12 on a natural law observation.⁴⁶² However, the claims merely recited this natural law without
13 reciting any novel application of it.⁴⁶³ The Court found that providing protection to such claims
14 would result in pre-empting “a broad range of potential uses” and excluding others from using
15

16 ⁴⁵⁸ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
17 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
18 statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 ⁴⁵⁹ Nor does the preceding paragraph, which provides only a purported summary of the claims of the '728 patent, or
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
21 grounds for Defendants’ allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,*
Inc. v. Garmin Int’l, Inc., 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
22 Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
23 early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
24 contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

⁴⁶⁰ *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.”).

⁴⁶¹ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

⁴⁶² *Mayo*, 132 S. Ct. at 1294.

⁴⁶³ *Id.* at 1301.

1 “the basic tools of scientific and technical work.”⁴⁶⁴ A method of treatment claim, specifying the
2 subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and
3 instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
4 protection.⁴⁶⁵

5 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
6 occurring substance. It is not. Even references contained within Defendants’ own contentions
7 make clear that EPA of the requisite purity and characteristics is not found in nature.⁴⁶⁶ As
8 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
9 decades it has been accepted that compositions isolated from nature or purified beyond their
10 natural state are patent-eligible.⁴⁶⁷ Moreover, Defendants’ assertions are immaterial to a Section
11 101 defense because method of treatment claims like the ones asserted in this case are patent
12 eligible even if they are directed to administration of a naturally occurring substance.⁴⁶⁸

13 To the extent Defendants are arguing that a law of nature both underlies the claims and
14 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
15 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁴⁶⁹ Since the

16 ⁴⁶⁴ *Id.*

17 ⁴⁶⁵ *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
18 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177 , 191-193 (1981) (upholding patentability
19 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
20 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
21 1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
22 eligible claims, such as method of treatment claims, would also be necessarily ineligible).

⁴⁶⁶ *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
23 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidation Contentions, *e.g.*, at 26–27).

⁴⁶⁷ *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
24 (CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

⁴⁶⁸ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

⁴⁶⁹ *See* Defendants’ Joint Invalidation Contentions at 199.

1 composition that is the subject of the claims is not naturally occurring, Defendants appear to
2 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
3 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
4 characterization of laws of nature.⁴⁷⁰ To say that the claims of the ’728 patent claim a law of
5 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
6 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
7 underlying principles of nature” that would “make all inventions unpatentable.”⁴⁷¹ Indeed, even
8 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
9 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁴⁷²

10 Even if there is some underlying law of nature in the asserted claims, the subject matter
11 of the ’728 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
12 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
13 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
14 foreclose from others the use of that equation in conjunction with all of the other steps in their
15 claimed process.’”⁴⁷³ As discussed above, the asserted claims of the ’728 patent contain a novel,
16
17

18 ⁴⁷⁰ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes to
19 achieve a desired outcome That one way of describing the process is to describe the natural ability of the
20 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).”).

21 ⁴⁷¹ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

22 ⁴⁷² See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
23 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

24 ⁴⁷³ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

1 unconventional, and specific method of treatment comprising a particularized application of a
2 nonnaturally occurring substance and does not preempt the use of a law of nature.⁴⁷⁴

3 Defendants also argue that any argument by Amarin in response to Defendants' § 112
4 arguments are further evidence of invalidity under § 101. This argument is without merit. The
5 claims are enabled and written description is satisfied for the reasons discussed below. In
6 addition, as discussed above, the asserted claims are not merely a naturally-occurring
7 phenomena, and thus satisfy the requirements of § 101.

8 **2. The Asserted Claims of the '728 Patent Are Not Anticipated by WO**
9 **'118**

10 To anticipate, a single prior art reference must sufficiently describe a claimed
11 invention so that the public is in "possession" of that invention.⁴⁷⁵ Therefore, to anticipate, a
12 reference must set forth every element of the claim, either expressly or inherently, in as complete
13 detail as is contained in the claim.⁴⁷⁶ The claim elements must also be "arranged" in the prior art
14 reference, just as they are in the claim,⁴⁷⁷ rather than as "multiple, distinct teachings that the
15 artisan might somehow combine to achieve the claimed invention."⁴⁷⁸ In addition, public
16 "possession" requires that the prior art enable a person of ordinary skill to make and use the
17

18 _____
19 ⁴⁷⁴ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
(rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
20 "just one step in the whole process" claimed by the invention).

21 ⁴⁷⁵ *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

22 ⁴⁷⁶ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
23 Cir. 1989).

24 ⁴⁷⁷ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

⁴⁷⁸ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

1 invention without undue experimentation.⁴⁷⁹ Factors that may be included in this analysis
2 include the quantity of experimentation necessary, the amount of direction or guidance
3 presented, the presence or absence of working examples, the nature of the invention, the state of
4 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
5 and the breadth of the claims.⁴⁸⁰ This inquiry is objective, and thus evidence of undue
6 experimentation need not be part of the prior art.⁴⁸¹

7 Defendants assert that Claims 1-19 of the '728 Patent are anticipated by the WO '118
8 reference.⁴⁸²

9 An element-by-element analysis, identifying each element of each asserted claim that is
10 absent from WO '118, is provided below. The contentions below are incorporated by reference
11 into Exhibit A, and vice-versa. WO '118 does not anticipate the claims of the '728 patent
12 because it does not describe, properly arrange, or enable the '728 patent claims.

13 a) WO '118 Does Not Teach Every Element of the Claims of the
14 '728 Patent

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

16 It is well established that, for a prior art reference to anticipate, "every element of the
17
18

19 ⁴⁷⁹ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

20 ⁴⁸⁰ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

21 ⁴⁸¹ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999 F.2d
22 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

23 ⁴⁸² References to "WO '118" are to the English translation that was filed with the European application. Plaintiffs
24 reserve their right to obtain a certified translation of WO '118.

1 | claimed invention must be identically shown in a single reference.”⁴⁸³ Moreover, the elements of
2 | the claimed invention must have “strict identity” with the elements of the reference; “minimal
3 | and obvious” differences are sufficient to prevent anticipation.⁴⁸⁴ Here, WO ‘118 entirely fails to
4 | disclose the following elements of Claim 1 of the ‘728 Patent: *to effect a reduction in*
5 | *triglycerides without substantially increasing LDL-C compared to a second subject having a*
6 | *fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the*
7 | *pharmaceutical composition and a concurrent lipid altering therapy.* WO ‘118 entirely fails to
8 | disclose the following elements of Claim 8 of the ‘728 Patent: *to effect a reduction in fasting*
9 | *triglycerides of at least about 15% without substantially increasing LDL-C compared to a*
10 | *second subject having fasting triglyceride of 500 mg/dl to about 1500 who has not received the*
11 | *pharmaceutical composition and concurrent lipid altering therapy.* WO ‘118 entirely fails to
12 | disclose the following elements of Claim 19 of the ‘728 Patent: *effective to reduce in a first*
13 | *patient population receiving 4 g per day of said composition without concurrent lipid altering*
14 | *therapy and having said baseline triglyceride level, a median triglyceride level by at least 5%*
15 | *without substantially increasing LDL-C, compared to a median triglyceride level and LDL-C*
16 | *level observed in a second patient population having said baseline triglyceride level who has not*
17 | *received the pharmaceutical composition and concurrent lipid altering therapy.* Defendants
18 | appear to concede that WO ‘118 does not expressly teach these elements, as they fail to set forth
19 | any basis for concluding that WO ‘118 teaches this element.⁴⁸⁵ Indeed, Defendants could not set
20 | forth any basis for concluding that WO ‘118 teaches this element because WO ‘118 does not.

22 | ⁴⁸³ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); see also *Hybritech Inc. v.*
Monoclonal Antibodies, Inc., 802 F.2d 1367 (Fed. Cir. 1986).

23 | ⁴⁸⁴ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 | ⁴⁸⁵ Defendants’ Invalidation Contentions at 202-204.

1 Instead, Defendants argue that these elements express the intended result of a method that
2 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
3 below, WO ‘118 fails to disclose each element of the independent claims of the ‘728 Patent,
4 either expressly or inherently. Therefore, WO ‘118 cannot anticipate the claimed method.
5 Defendants also argue that these elements represent inherent, natural properties of EPA, and are
6 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of
7 anticipation and claim construction. Further, while Defendants argue that the inherent properties
8 are exemplified in the prior art, they fail to identify even a single prior art reference that makes
9 such a disclosure. Defendants cannot point to a single, specific prior art reference because the
10 claimed pharmaceutical composition has never been administered in the manner claimed to the
11 claimed patient population. Also, these elements are positively recited in the body of the claim
12 and therefore cannot be construed as a non-limiting preamble and must be given patentable
13 weight.

14 Further, Defendants entirely fail to prove that WO ‘118 inherently discloses the claimed
15 lipid effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
16 inherently anticipate as a matter of law.”⁴⁸⁶ “[A]nticipation by inherent disclosure is appropriate
17 only when the reference discloses prior art that must *necessarily* include the unstated
18 limitation.”⁴⁸⁷ “It is not sufficient if a material element or limitation is ‘merely probably or
19 possibly present’ in the prior art.”⁴⁸⁸ WO ‘118 fails to provide any data related to the lipid
20 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
21

22 ⁴⁸⁶ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁴⁸⁷ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁴⁸⁸ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

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

3 Defendants fail to demonstrate that administration of the claimed EPA compositions
4 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants
5 suggests that EPA administration may increase LDL-C.⁴⁸⁹ Rambjor is a clinical study which
6 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
7 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
8 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
9 decrease TG without increasing LDL-C *every time it is administered*.

10 Therefore, WO ‘118 cannot anticipate the independent claims of the ‘728 patent.
11 Because the dependent claims include all of the claim elements of the independent claims, WO
12 ‘118 cannot anticipate any of the dependent claims as well.

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

15 In addition, WO ‘118 fails to disclose or suggest the claimed pharmaceutical composition
16 be administered in the manner claimed to the claimed patient population. Defendants attempt to
17 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is
18 the introductory clause of a patent claim and includes everything from the beginning of the claim
19 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the
20 preamble.

21 A claim preamble has patentable weight if, “when read in the context of the entire claim,
22 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,

23 _____
24 ⁴⁸⁹ See, e.g., Rambjor.

1 and vitality’ to the claim.”⁴⁹⁰ Additionally, the preamble constitutes a claim element when the
2 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
3 claim body to define the claimed limitation.”⁴⁹¹

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

8 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
9 properly construed as a limitation of the claim itself.”⁴⁹² The recitation of a “method of reducing
10 triglycerides” in the preamble provides antecedent basis for the effect of reducing triglycerides in
11 the body of the claim and emphasizes the intentional purpose for which the method must be
12 performed - to reduce triglycerides.

13 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
14 to define the subject matter of the claimed invention.”⁴⁹³ Thus, the entire preamble in the
15 independent claims of the ‘728 must contain patentable weight.

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

20 ⁴⁹⁰ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 ⁴⁹¹ *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 ⁴⁹² *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
23 computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

24 ⁴⁹³ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact,
2 the invention disclosed by WO '118 relates to a composition for preventing occurrence of
3 cardiovascular events, as evidenced by the title which reads "Composition for Preventing the
4 Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence
5 of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and
6 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
7 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
8 angina and exercise-induced angina, and destabilization of the angina."⁴⁹⁴ The invention of WO
9 '118 is intended to be administered to any person in need of prevention of the occurrence of
10 cardiovascular events, who are typically hypercholesterolemia patients.⁴⁹⁵ WO '118 does not
11 expressly describe its invention as a "method of reducing triglycerides," therefore it cannot
12 anticipate the independent claims.

13 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail
14 to prove that these elements of the claimed invention have "strict identity" with the elements of
15 the reference.⁴⁹⁶ WO '118 fails to anticipate this claim element because the broad disclosure
16 fails to anticipate the narrow claimed range, and the specific patient population defined in the
17 claims is an essential part of the claimed invention.

18 There is no evidence in WO '118 that subject as described in the claims were ever
19 treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants
20 rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses
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22 ⁴⁹⁴ WO '118 at 12.

23 ⁴⁹⁵ *Id.*

24 ⁴⁹⁶ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 treatment of the subject as described in the claims. It does not. Defendants’ argument rests on
2 the definition in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at
3 least 150 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working
4 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels
5 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
6 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as
7 evidence that a “person of ordinary skill in the art would have understood that the term
8 ‘hypertriglyceridemia’ when used in the WO ‘118 includes patients with triglyceride levels of
9 500 mg/dL to about 1500 mg/dL.” The cited section states that “soft capsules” are preferable
10 and then merely provides examples of commercially available “soft capsules,” such as Omacor.
11 The passage does not define “hypertriglyceridemia” as used in WO ‘118 as referring to patients
12 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
13 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’ or
14 ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”⁴⁹⁷ Therefore,
15 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
16 ‘118 meets the claim elements of the independent claims every time it is administered.

17 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges
18 claimed by the ‘728 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
19 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
20 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
21 claimed temperature range, “[g]iven the considerable difference between the claimed range and
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23 ⁴⁹⁷ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).
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1 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
2 claimed range with sufficient specificity to anticipate this element of the claim.”⁴⁹⁸ A prior art’s
3 teaching of a broad genus does not necessarily disclose every species within that genus. The
4 court explained the slightly overlapping range between the preferred range and claimed range “is
5 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁴⁹⁹ and therefore
6 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
7 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
8 anticipate the subject as described in the claims because it fails to described the claimed TG
9 range with sufficient specificity.

10 The court in *Atofina* ruled on an additional question of anticipation that also involved a
11 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
12 compared to the patent’s claimed range of 0.1 to 5.0 percent.⁵⁰⁰ The court explained that
13 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
14 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
15 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”⁵⁰¹ Similarly,
16 although there may be overlap between the definition of hypertriglyceridemia taught by WO
17 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
18 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500
19 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of
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21 ⁴⁹⁸ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

22 ⁴⁹⁹ *Atofina*, 441 F.3d at 1000.

23 ⁵⁰⁰ *Id.*

24 ⁵⁰¹ *Id.*

1 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
2 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
3 events as the primary clinical objective),⁵⁰² WO '118, therefore, does not expressly disclose the
4 specific patient population that is an essential element of the claims of the asserted patents.
5 Therefore, WO '118 cannot anticipate the claims of the asserted patents.

6 The treatment of a patient with elevated TG levels varies depending on their serum
7 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
8 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
9 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
10 of lipid disorders.⁵⁰³ The ATP-III divided hypertriglyceridemia patients into three classes based
11 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
12 and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment
13 strategies for patients depending on classification.⁵⁰⁴ For the borderline-high and high TG
14 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.⁵⁰⁵
15 Accordingly, in these populations, physicians focused on lowering LDL-C.⁵⁰⁶ In this patient
16 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
17 In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of
18 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated
19 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary

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21 ⁵⁰² See Section III.

22 ⁵⁰³ *Id.*

23 ⁵⁰⁴ ATP III at 3335; *See also* Section III.

24 ⁵⁰⁵ *Id.*

⁵⁰⁶ *Id.*

1 treatment goal.⁵⁰⁷ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
2 were considered fundamentally different from patients with borderline-high or high TGs from a
3 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

4 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
5 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
6 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
7 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
8 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
9 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels
10 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
11 decreasing triglycerides), as required by the independent claims of the asserted patents, and
12 therefore cannot anticipate the independent claims of the ‘728 Patent.

13 Third, WO ‘118 fails to disclose the claim element of “a subject . . . who does not receive
14 concurrent lipid altering therapy.” Defendants’ only basis for concluding that WO ‘118 teaches
15 this element is that WO ‘118 “discloses and claims the administration of EPA-E without the
16 administration in combination with statins.”⁵⁰⁸ This sentence appears to be incomplete, as it is
17 unclear what Defendants mean by “without the administration in combination with statins.” This
18 single statement, without citation to a single page in WO ‘118, fails to demonstrate that WO ‘118
19 teaches this element. In fact, WO ‘118 methods comprise statins, i.e. HMG-CoA RI.⁵⁰⁹

21 ⁵⁰⁷ *Id.*

22 ⁵⁰⁸ Defendants’ Invalidation Contentions at 46.

23 ⁵⁰⁹ HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of
24 drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

1 WO '118 states that its disclosed composition is “effective in preventing occurrence of
2 cardiovascular events in hypercholesterolemia patients, and in particular, in preventing
3 occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with
4 HMG-CoA RI but still suffer from the risk of the cardiovascular events.”⁵¹⁰ WO '118 goes on to
5 state that the “effect of the composition of the present invention will be synergistically improved
6 by combined use with the HMG-CoA RI, and such use of the composition of the present
7 invention with the HMG-CoA RI has clinical utility since the effect of preventing the
8 cardiovascular event occurrence is expected to be improved.”⁵¹¹ Administering the composition
9 of WO '118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-
10 CoA RI has on the disclosed compound. Further, WO '118 teaches that the disclosed
11 composition may be used with a long list of other drugs, including lipid altering drugs such as
12 antilipotropic drugs and fibrate drugs.⁵¹² Thus, WO '118 does not disclose administration of the
13 claimed EPA compositions to a subject that has very high TG levels and also “does not receive
14 concurrent lipid altering therapy” and cannot anticipate the independent claims of the '728
15 patent. In fact, the example of the methods of WO '118 expressly teaches a statin/EPA co-
16 therapy. Because the dependent claims depend from the independent claims, they include the
17 elements of the independent claims. Thus, WO '118 cannot anticipate any of the dependent
18 claims of the '728 patent.

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⁵¹⁰ WO '118 at 9 (emphasis added).

23 ⁵¹¹ *Id.* at 10.

24 ⁵¹² *Id.* at 24-25.

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

3 WO '118 further does not anticipate the claims of the '728 patent because it does not
4 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as
5 claimed, it cannot anticipate oral administration to the claimed "subject."

6 WO '118 additionally cannot anticipate the claims of the '728 patent because it does not
7 disclose administering the pharmaceutical composition at a dose of about 4g per day.
8 Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is
9 "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which
10 states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more
11 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
12 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is
13 not particularly limited as long as the intended effect, preventing the occurrence of
14 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
15 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
16 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
17 working examples, data or other reference in WO '118 indicating that any subject (much less
18 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
19 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

20 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
21 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
22 court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic
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1 range of 330 to 450 °C,”⁵¹³ and therefore failed to anticipate the claimed range. The court in
2 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
3 the patent’s claimed range of 0.1 to 5.0 percent.⁵¹⁴ The court explained that “although there is a
4 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
5 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
6 different, not the same. . . . Thus, there is no anticipation.”⁵¹⁵ Similarly, although there may be
7 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘728
8 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range
9 claimed by the ‘728 patent does not fall within WO ‘118’s preferred range. Defendants
10 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,
11 the example indicates that up to 900 mg of the EPA composition could be used three times per
12 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘728
13 patent and cannot anticipate the independent claims of the ‘728 Patent.

14 WO ‘118 further does not anticipate the claims of the ‘728 patent because it does not
15 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
16 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.
17 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high
18 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
19 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
20 higher, and still more preferably 96.5% by weight or higher.”⁵¹⁶ Therefore, WO ‘118 discloses

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22 ⁵¹³ *Atofina*, 441 F.3d at 1000.

23 ⁵¹⁴ *Id.*

24 ⁵¹⁵ *Id.*

⁵¹⁶ WO ‘118 at 22.

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

4 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the
5 . . . range claimed in the” patent is insufficient for anticipation.⁵¹⁷ In *Atofina*, the prior art
6 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
7 range between 330 and 450 degrees. The court explained that this slight overlap “is not
8 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”⁵¹⁸ and therefore failed
9 to anticipate the claimed range.⁵¹⁹ The court in *Atofina* also found that a prior art disclosure of a
10 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
11 percent.⁵²⁰ The court explained that “although there is a slight overlap, no reasonable fact finder
12 could determine that this overlap describes the entire claimed range with sufficient specificity to
13 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
14 anticipation.”⁵²¹

15 Similarly, although there may be some overlap between the E-EPA content disclosed by
16 WO ‘118 and the ranges claimed by the ‘728 patent, WO ‘118 does not specifically highlight the
17 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
18 critical factor of the invention disclosed in the ‘728 patent. Therefore, WO ‘118’s broad
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21 ⁵¹⁷ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

22 ⁵¹⁸ *Atofina*, 441 F.3d at 1000.

23 ⁵¹⁹ *Atofina*, 441 F.3d at 1000.

24 ⁵²⁰ *Id.*

⁵²¹ *Id.*

1 disclosure of the E-EPA content in its invention does not describe the claimed range with
2 sufficient specificity and cannot anticipate the independent claims of the '728 patent.

3 WO '118 is additionally insufficient for anticipation because it does not expressly
4 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118
5 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is
6 DHA-E."⁵²² The disclosure goes on to state that the composition of the invention is preferably
7 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
8 pharmaceutical composition is a critical factor of the invention disclosed in the '728 patent.

9 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed
10 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
11 There is no express teaching or guidance directing the person of ordinary skill in the art to the
12 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
13 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
14 claims of the '728 patent.

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

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⁵²² WO '118 at 22.

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

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

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

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

1 inherently anticipate as a matter of law.”⁵²³ “[A]nticipation by inherent disclosure is appropriate
2 only when the reference discloses prior art that must *necessarily* include the unstated
3 limitation.”⁵²⁴ “It is not sufficient if a material element or limitation is ‘merely probably or
4 possibly present’ in the prior art.”⁵²⁵ Defendants fail to show that WO ‘118 “*necessarily*” meets
5 the recited claim elements relating to the administration step, the dosage form or characteristics
6 of the treated subject and the specific effect produced by the claimed method *every time*. WO
7 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
8 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
9 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,
10 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
11 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim
12 elements.

13 3. The Claims of the ‘728 Patent Would Not Have Been Obvious In 14 Light of the Asserted References

15 Defendants identify 77 separate references that it asserts somehow render the claims of
16 the ‘728 Patent obvious.⁵²⁶ Defendants fail to demonstrate by clear and convincing evidence that
17 any of these references, alone or in combination, would render obvious any claims of the ‘728
18 Patent. Defendants’ arguments rely on hindsight by impermissibly using the blueprint of the
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21 ⁵²³ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

22 ⁵²⁴ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 ⁵²⁵ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 ⁵²⁶ Defendants’ Joint Invalidity Contentions at 13-25.

1 '728 Patent itself to guide its combination of references.⁵²⁷ Defendants chart a laundry list of 77
2 separate references, without explanation. Defendants' disclosures do not comply with Local
3 Patent Rule 1-8 and fail to put Plaintiffs on notice of how these references allegedly establish
4 that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot
5 respond to undisclosed combinations and arguments.⁵²⁸

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

- 9 • 1) “. . .the asserted claims of the '728 patent would have been obvious over the
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
11 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
12 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
13 2000 (and/or Satoh or Shinozaki in view of Contacos).”
- 14 • 2) “. . .the asserted claims of the '728 patent would have been obvious over the
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
16 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
17 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
18 2000 and/or Maki.”
- 19 • 3) “. . .the asserted claims of the '728 patent would have been obvious over the
20 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
21 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
22 of Satoh or Shinozaki in further view of Contacos.”
- 23 • 4) “. . . the asserted claims of the '728 patent would have been obvious over WO '118
24 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the
Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”

20 ⁵²⁷ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is
obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 ⁵²⁸ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
rely on undisclosed or insufficiently disclosed references or argument.

- 1
- 2 • 5) “. . . the asserted claims of the ’728 patent would have been obvious over WO
 - 3 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
 - 4 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
 - 5 further in view of Katayama, Matsuzawa and/or Takaku.”

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

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

8 the time the invention was made to a person having ordinary skill in the art.”⁵²⁹ Obviousness is a

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

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

11 claims at issue.⁵³⁰

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

13 teaches, including the portions that would lead away from the claimed invention.⁵³¹ Indeed, any

14 teaching in the art that points away from the claimed invention must be considered.⁵³² A

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

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

17 divergent from the path that was taken by the applicant.⁵³³ For instance, a reference teaches

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

19 unlikely to be productive of the result sought by the applicant.⁵³⁴

20 ⁵²⁹ 35 U.S.C. § 103(a).

21 ⁵³⁰ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

22 ⁵³¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁵³² *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

24 ⁵³³ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

⁵³⁴ *Id.*

1 In order to find obviousness based on a combination of references, there must be some
2 rationale for combining the references in the way claimed that is separate and apart from the
3 hindsight provided by the patented invention itself.⁵³⁵ The law prohibits an obviousness
4 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
5 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
6 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
7 invention.”⁵³⁶ “The invention must be viewed not after the blueprint has been drawn by the
8 inventor, but as it would have been perceived in the state of the art that existed at the time the
9 invention was made.”⁵³⁷

10 “The determination of obviousness is made with respect to the subject matter as a whole,
11 not separate pieces of the claim.”⁵³⁸ “[A] patent composed of several elements is not proved
12 obvious merely by demonstrating that each of its elements was, independently, known in the
13 prior art.”⁵³⁹ “This is so because inventions in most, if not all, instances rely upon building
14 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
15 of what, in some sense, is already known.”⁵⁴⁰

16 Accordingly, it is improper to pick and choose isolated elements from the prior art and
17 combine them so as to yield the invention⁵⁴¹ or to modify a prior art reference in a way that

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19 ⁵³⁵ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

20 ⁵³⁶ See *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983).

21 ⁵³⁷ *Sensonic, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996).

22 ⁵³⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

23 ⁵³⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

24 ⁵⁴⁰ *KSR*, 550 U.S. at 418–419.

⁵⁴¹ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

1 “would destroy the fundamental characteristics of that reference.”⁵⁴² Moreover, a combination is
2 not obvious where “it would be impossible to apply these teachings [of the secondary reference]
3 to the [primary reference] without entirely changing the basic mechanism and procedure
4 thereof,”⁵⁴³ or where the proposed combination requires “material and radical modification in
5 order to conform to [the patentee’s] claims” or a “total reconstruction” of the prior art device.⁵⁴⁴
6 Furthermore, it is improper “to modify the secondary reference before it is employed to modify
7 the primary reference” in assessing obviousness.⁵⁴⁵

8 Further, a party asserting obviousness in view of a combination of prior art disclosures
9 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
10 combine the elements in the manner claimed⁵⁴⁶ and “a reasonable expectation of success.”⁵⁴⁷

11 For chemical compounds, there must have been a reason both to select the prior art
12 compound “most promising to modify” and to make the necessary changes to arrive at the
13 claimed compound.⁵⁴⁸ This protects against the use of hindsight to pick through the prior art
14

15 ⁵⁴² *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

16 ⁵⁴³ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958).

17 ⁵⁴⁴ *Id.* at 88.

18 ⁵⁴⁵ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957).

19 ⁵⁴⁶ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 ⁵⁴⁷ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

23 ⁵⁴⁸ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
24 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

1 based solely on structural similarity to the claimed compound.⁵⁴⁹ Any assertion of an “apparent
2 reason” must find a basis in the factual record.⁵⁵⁰

3 The “reasonable expectation of success” for a chemical compound must be of all of a
4 claimed compound’s relevant properties,⁵⁵¹ including those discovered after the patent was filed
5 or even issued.⁵⁵² “The basic principle behind this rule is straight-forward—that which would
6 have been surprising to a person of ordinary skill in a particular art would not have been
7 obvious.”⁵⁵³ Any assertion of a “reasonable expectation of success” must find a basis in the
8 factual record.⁵⁵⁴

9
10 ⁵⁴⁹ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381 Fed. App'x.
11 985, 994 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed.
12 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.
13 2002).

14 ⁵⁵⁰ *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
19 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed
20 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438 F.
21 Supp. 2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
22 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
23 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
24 motivated to resolve citalopram in June 1988”).

25 ⁵⁵¹ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
26 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
27 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
28 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d
29 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine Here, the
30 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
31 pharmacological properties that it possesses.”).

32 ⁵⁵² *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F. Supp. 2d at
33 908.

34 ⁵⁵³ *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.”).

⁵⁵⁴ *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

1 In an obviousness determination, any objective indicia of nonobviousness must be taken
2 into account.⁵⁵⁵ An objective indicium is any “event[] proved to have actually happened in the
3 real world” that evidences the nonobvious nature of the invention.⁵⁵⁶ The existence of an
4 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
5 surprising results, expressions of skepticism, industry praise, commercial success, and copying
6 are classical indicia of nonobviousness.⁵⁵⁷ These factual inquiries “guard against slipping into
7 use of hindsight,”⁵⁵⁸ and “may often be the most probative and cogent evidence of
8 nonobviousness.”⁵⁵⁹

9 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
10 have been fully “in possession” of the public—which requires that the claimed invention have
11 been enabled.⁵⁶⁰

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

21 ⁵⁵⁵ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *Jones v. Hardy*, 727 F.2d 1524, 1530–31 (Fed. Cir. 1984).

22 ⁵⁵⁶ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

23 ⁵⁵⁷ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*
24 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

⁵⁵⁸ *Graham*, 383 U.S. at 36.

⁵⁵⁹ *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)).

⁵⁶⁰ *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

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

4 a) General Overview

5 Defendants fail to provide a single prior art reference that discloses administration of the
6 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
7 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
8 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
9 concentrations, in a wide range of doses and administration periods, to subjects who have
10 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
11 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
12 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
13 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
14 distinguish between the effect of the placebo from that of the active agent. Studies which
15 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
16 independent effects of EPA and DHA.⁵⁶¹ Inconsistency in dosages and administration periods
17 and variations in the administered fatty acid compositions also complicate the interpretation of
18 the results and limit the application of these studies.

19 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
20 very high TGs together with patients with high and borderline high TGs indicates that there is no
21 medical difference in responsiveness to treatment among the groups of people.”⁵⁶² Defendants
22

23 ⁵⁶¹ Mori 2006 at 96.

24 ⁵⁶² Defendants’ Joint Invalidity Contentions at 211 (*see* FN 26).

1 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
2 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
3 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
4 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
5 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
6 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
7 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.⁵⁶³ In
8 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
9 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
10 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
11 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
12 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
13 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
14 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical
15 difference in responsiveness to treatment between the very-high TG patient population and lower
16 TG patient populations merely because there was possibly one patient with baseline TG levels of
17 at least 500 mg/dL.

18 As discussed above in Section III, patients with very-high TG levels were considered
19 fundamentally different from patients with borderline-high or high TGs from a clinical,
20 regulatory, and therapeutic perspective.⁵⁶⁴ Clinically, the authoritative guidance to physicians on
21

22 ⁵⁶³ FDA Briefing Document, Oct. 16, 2013 at 26 (The mean baseline TG value for the placebo group was 270.6
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL.).

24 ⁵⁶⁴ See Bays Jan. 8, 2012 Decl., ¶ 20.

1 the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-
2 III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high
3 TG; and very high TG. The primary risk faced by borderline-high and high TG patients was
4 atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis.
5 Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and
6 high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients
7 was TG reduction. This distinction between patients with borderline-high/high TG levels and
8 patients with very high TG levels is also observed on the regulatory level. The FDA recognized
9 the different clinical status of the very-high TG population by approving some drugs specifically
10 for the very-high TG group without granting treatment indications for the borderline-high or high
11 TG populations (i.e. Lovaza/Omacor).⁵⁶⁵

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

18 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
19 *increase* LDL-C in very-high TG patients.⁵⁶⁶ The fibrate Tricor (fenofibrate), for example,
20 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)⁵⁶⁷

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22 ⁵⁶⁵ See Bays Jan. 8, 2012 Decl., ¶ 22.

23 ⁵⁶⁶ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain
roughly the same in high TG group, and increase by around 50% in the very-high TG group).

24 ⁵⁶⁷ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

1 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).⁵⁶⁸ In
 2 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
 3 significant increase in LDL-C was observed.⁵⁶⁹ In patients with very-high TGs (mean baseline
 4 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).⁵⁷⁰ Similar results
 5 were seen with the administration of Lopid (gemfibrozil).⁵⁷¹ The differing effects of fibrates,
 6 such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values demonstrates
 7 how a person of ordinary skill at the time of the invention would have understood that one could
 8 not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients
 9 with normal, borderline-high or high TG levels would be the same in patients with very-high TG
 10 levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-
 11 499 mg/dL). As illustrated in the table, below, patients with normal or high baseline TG levels
 12 experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate,
 13 Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and
 14 patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience
 15 significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ⁵⁷²	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*

⁵⁶⁸ *Id.*

⁵⁶⁹ *Id.* See also, Trilipix Label at 27.

⁵⁷⁰ *Id.* See also, Trilipix Label at 27.

⁵⁷¹ 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).

⁵⁷² 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.⁵⁷³ It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.⁵⁷⁴ 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%.⁵⁷⁵ Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁵⁷⁶

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

⁵⁷³ Chan 2002 I at 2379-81.

⁵⁷⁴ *Id.*; *See also*, Westphal at 918.

⁵⁷⁵ *See* Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; *see also*, Lovaza PDR and Omacor PDR.

⁵⁷⁶ *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.)”

1 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
2 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
3 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
4 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
5 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
6 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
7 VLDL particle conversion.⁵⁷⁷ Because normal to high TG patients did not have the large
8 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
9 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
10 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
11 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
12 highest baseline TG levels⁵⁷⁸ and did not increase for patients with lower TG levels. Therefore,
13 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
14 borderline-high or high TG patients was *expected*.

15 Defendants contend that “a composition and its properties are inseparable, and therefore
16 do not impart any additional patentability,” and that “all of the limitations regarding the
17 properties of the ethyl EPA compound identified in the claims of the ‘728 patent are inherent to
18 the compound when administered to a human subject.”⁵⁷⁹ Inherency may not supply a missing

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20 ⁵⁷⁷ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
21 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
22 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
decrease in VLDL.”).

23 ⁵⁷⁸ Bays 2008 I at 400-402.

24 ⁵⁷⁹ Defendants’ Joint Invalidity Contentions at 212.

1 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
2 of ordinary skill in the art.⁵⁸⁰ Obviousness is based on what is *known* in the art at the time of the
3 invention.⁵⁸¹ It was not known or reasonably expected at the time of the claimed invention that
4 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
5 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and
6 Apo-B necessarily present, or the natural result of the combination of elements explicitly
7 disclosed by the prior art.⁵⁸² Therefore, inherency does not supply the missing claim elements in
8 the prior art cited by Defendants.

9 Defendants argue that the claims of the ‘728 patent which contain “a limiting clause, such
10 as ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step positively
11 recited and therefore are not elements.⁵⁸³ This is incorrect. “There is nothing inherently wrong
12 with defining some part of an invention in functional terms.”⁵⁸⁴ When a clause “states a
13 condition that is material to patentability, it cannot be ignored in order to change the substance of
14 the invention.”⁵⁸⁵ The claim term “to effect” acts as a positive limitation if the term represents

17 ⁵⁸⁰ See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
18 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
19 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

20 ⁵⁸¹ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) (“That which may be inherent is not necessarily known.
Obviousness cannot be predicated on what is unknown.”).

21 ⁵⁸² See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 ⁵⁸³ Defendants’ Joint Invalidity Contentions at 212.

23 ⁵⁸⁴ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ⁵⁸⁵ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

1 “unexpected and improved effects of administration of the claimed compound.”⁵⁸⁶ In addition,
2 the elements represent unexpected and improved effects of administration of purified EPA,
3 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
4 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the
5 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
6 patentable weight.

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

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

16 (1) WO ‘118

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

19 Defendants assert that certain cited sections of WO ‘118 disclose or suggest elements of
20 the ‘728 Claims. The cited portions of WO ‘118 do not disclose or suggest these elements at
21 least because they do not disclose or suggest administration of EPA with the recited purity to a
22 subject with the recited very high TG levels who does not receive concurrent lipid altering

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24 ⁵⁸⁶ *AstraZeneca AB v. Dr. Reddy’s Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11–12 (D.N.J. May 18, 2010).

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

5 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
6 WO '118 does not disclose or suggest a subject with the recited very high TG levels who does
7 not receive concurrent lipid altering therapy. WO '118 also does not disclose or suggest the
8 claimed pharmaceutical composition with the recited fatty acids compositions or dosage. WO
9 '118 further does not disclose or suggest a method to effect the recited TG reduction without
10 substantially increasing LDL-C. Further, with respect to Claims 1 and 8, WO '118 does not
11 disclose or suggest the recited effect based on a comparison to a second subject having the
12 recited very high TG levels who has not received the pharmaceutical composition and a
13 concurrent lipid altering therapy. With respect to Claim 19, WO '118 does not disclose or
14 suggest a method that is effective to reduce the recited very high TG levels without substantially
15 increasing LDL-C in a first patient population with the recited very high TG levels receiving the
16 recited dosage of the recited pharmaceutical composition without concurrent lipid altering
17 therapy, based on a comparison to a second patient population with the recited very high TG
18 levels who has not received the pharmaceutical composition and concurrent lipid altering
19 therapy.

20 Further, with respect to Claims 4 and 11, this reference fails to disclose or suggest the
21 subject and the second subject having the recited baseline lipid levels. With respect to Claims 5
22 and 12, this reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in
23 the subject with the claimed TG levels based on a comparison to the second subject. With
24

1 respect to Claims 6 and 13, this reference fails to disclose or suggest the recited reduction in TG
2 in the subject with the claimed TG levels based on a comparison to the second subject. With
3 respect to Claims 7 and 14, this reference fails to disclose or suggest the recited reduction in
4 fasting Lp-PLA2 in the subject with the claimed TG levels based on a comparison to the second
5 subject. With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject
6 and second subject consume a Western diet. With respect to Claims 16 and 18, this reference
7 fails to disclose or suggest the pharmaceutical composition with the recited fatty acid
8 composition.

9 (2) WO '900

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

11 Defendants assert that certain cited sections of WO '900 disclose or suggest elements of
12 the '728 Claims. The cited portions of WO '900 do not disclose or suggest these elements at
13 least because they do not disclose or suggest administration of EPA with the recited purity to a
14 subject with the recited very high TG levels who does not receive concurrent lipid altering
15 therapy. The cited portions of WO '900 further do not disclose or suggest the claimed
16 pharmaceutical composition with the recited dosage or administration period. The cited portions
17 of WO '900 further do not disclose or suggest a method to effect the recited TG reduction
18 without substantially increasing LDL-C.

19 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
20 WO '900 does not disclose or suggest a subject with the recited very high TG levels who does
21 not receive concurrent lipid altering therapy. WO '900 also does not disclose or suggest the
22 claimed pharmaceutical composition with the recited fatty acid dosage or administration period.
23 WO '900 further does not disclose or suggest a method to effect the recited TG reduction without
24 substantially increasing LDL-C. Further, with respect to Claims 1 and 8, WO '900 does not

1 disclose or suggest the recited effect based on a comparison to a second subject having the
2 recited very high TG levels who has not received the pharmaceutical composition and a
3 concurrent lipid altering therapy. With respect to Claim 19, WO '900 does not disclose or
4 suggest a method that is effective to reduce the recited very high TG levels without substantially
5 increasing LDL-C in a first patient population with the recited very high TG levels receiving the
6 recited dosage of the recited pharmaceutical composition without concurrent lipid altering
7 therapy, based on a comparison to a second patient population with the recited very high TG
8 levels who has not received the pharmaceutical composition and concurrent lipid altering
9 therapy.

10 Further, with respect to Claims 2 and 9, this reference does not disclose or suggest
11 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 11, this
12 reference fails to disclose or suggest the subject and the second subject having the recited
13 baseline lipid levels. With respect to Claims 5 and 12, this reference fails to disclose or suggest
14 the recited non-HDL-C and VLDL-C effects in the subject with the claimed TG levels based on a
15 comparison to the second subject. With respect to Claims 6 and 13, this reference fails to
16 disclose or suggest the recited reduction in TG in the subject with the claimed TG levels based
17 on a comparison to the second subject. With respect to Claims 7 and 14, this reference fails to
18 disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject with the claimed TG
19 levels based on a comparison to the second subject. With respect to Claims 15 and 17, this
20 reference fails to disclose or suggest the subject and second subject consume a Western diet.
21 With respect to Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical
22 composition with the recited fatty acid composition.

23
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CONFIDENTIAL

1 (3) Contacos

2 Contacos describes a study designed to determine the safety and efficacy of a statin
3 (pravastatin) combined with fish oil either alone or in combination, for the management of
4 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in
5 the claims. Contacos also notes that increases in LDL-C as a consequence of fish oil therapy
6 were known and describes the state of the art of treating mixed hyperlipidemias as of 1993.
7 “Improved forms of treatment for mixed hyperlipidemias are required because the only available
8 monotherapy that effectively reduces both TC and TG levels, nicotinic acid, is difficult to
9 tolerate and may exacerbate hyperuricemia, glucose intolerance, and hepatic dysfunction.” “until
10 now there have been limited options for safe and effective treatment of the simultaneous
11 elevation of both cholesterol and TGs that occurs in mixed hyperlipidemia.” Contacos attributes
12 the observed reduction of LDL-C after administration of fish oil to pravastatin and notes that
13 pravastatin reversed “the elevation in LDL-C associated with fish-oil therapy.”

14 Defendants assert that certain cited sections of Contacos disclose or suggest elements of
15 the ‘728 Claims. The cited portions of Contacos do not disclose or suggest these elements at
16 least because they do not disclose or suggest administration of EPA with the recited purity to a
17 subject with the recited very high TG levels who does not receive concurrent lipid altering
18 therapy. The cited portions of Contacos further do not disclose or suggest the claimed
19 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
20 period. The cited portions of Contacos further do not disclose or suggest a method to effect the
21 recited TG reduction without substantially increasing LDL-C.

22 With respect to Claims 1, 8 and 19 of the ‘728 Patent (and therefore all asserted claims),
23 Contacos does not disclose or suggest a subject with the recited very high TG levels who does
24 not receive concurrent lipid altering therapy. Contacos also does not disclose or suggest the

1 claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
2 administration period. Contacos further does not disclose or suggest a method to effect the
3 recited TG reduction without substantially increasing LDL-C. Further, with respect to Claims 1
4 and 8, Contacos does not disclose or suggest the recited effect based on a comparison to a second
5 subject having the recited very high TG levels who has not received the pharmaceutical
6 composition and a concurrent lipid altering therapy. With respect to Claim 19, Contacos does
7 not disclose or suggest a method that is effective to reduce the recited very high TG levels
8 without substantially increasing LDL-C in a first patient population with the recited very high
9 TG levels receiving the recited dosage of the recited pharmaceutical composition without
10 concurrent lipid altering therapy, based on a comparison to a second patient population with the
11 recited very high TG levels who has not received the pharmaceutical composition and concurrent
12 lipid altering therapy.

13 Further, with respect to Claims 2 and 9, this reference does not disclose or suggest
14 administration to the subject 1 to 4 times per day. With respect to Claims 5 and 12, this
15 reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in the subject
16 based on a comparison to the second subject. With respect to Claims 6 and 13, this reference
17 fails to disclose or suggest the recited reduction in TG in the subject based on a comparison to
18 the second subject. With respect to Claims 7 and 14, this reference fails to disclose or suggest
19 the recited reduction in fasting Lp-PLA2 in the subject based on a comparison to the second
20 subject. With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject
21 and second subject consume a Western diet. With respect to Claims 16 and 18, this reference
22 fails to disclose or suggest the pharmaceutical composition with the recited fatty acid
23 composition.

24
CONFIDENTIAL

1 (4) Grimsgaard

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

6 Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements
7 of '728 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at
8 least because they do not disclose or suggest administration of EPA with the recited purity to a
9 subject with the recited very high TG levels who does not receive concurrent lipid altering
10 therapy. The cited portions of Grimsgaard further do not disclose or suggest the claimed
11 pharmaceutical composition with the recited fatty acid compositions or administration period.

12 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
13 Grimsgaard does not disclose or suggest a subject with the recited very high TG levels who does
14 not receive concurrent lipid altering therapy. Grimsgaard also does not disclose or suggest the
15 claimed pharmaceutical composition with the recited fatty acid compositions or administration
16 period. With respect to Claim 19, Grimsgaard does not disclose or suggest a method that is
17 effective to reduce the recited very high TG levels without substantially increasing LDL-C in a
18 first patient population with the recited very high TG levels receiving the recited dosage of the
19 recited pharmaceutical composition without concurrent lipid altering therapy, based on a
20 comparison to a second patient population with the recited very high TG levels who has not
21 received the pharmaceutical composition and concurrent lipid altering therapy.

22 Further, with respect to Claims 5 and 12, this reference fails to disclose or suggest the
23 recited non-HDL-C and VLDL-C effects in the subject based on a comparison to the second
24 subject. With respect to Claims 6 and 13, this reference fails to disclose or suggest the recited

1 reduction in TG in the subject based on a comparison to the second subject. With respect to
2 claims 7 and 14, this reference fails to disclose or suggest the recited reduction in fasting Lp-
3 PLA2 in the subject based on a comparison to the second subject. With respect to Claims 15 and
4 17, this reference fails to disclose or suggest the subject and second subject consume a Western
5 diet. With respect to Claims 16 and 18, this reference fails to disclose or suggest the
6 pharmaceutical composition with the recited fatty acid composition.

7 (5) Hayashi

8 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
9 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
10 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride
11 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220
12 mg/dl.

13 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
14 '728 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
15 administration of EPA with the recited purity to a subject with the recited very high TG levels
16 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
17 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or
18 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
19 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
20 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
21 high TG levels.

22 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
23 Hayashi does not disclose or suggest a subject with the recited very high TG levels who does not
24 receive concurrent lipid altering therapy. Hayashi also does not disclose or suggest the claimed

1 pharmaceutical composition with the recited fatty acid compositions or administration period.
2 Hayashi further does not disclose or suggest a method to effect the recited TG reduction without
3 substantially increasing LDL-C in patients with very high TGs. Further, with respect to Claims 1
4 and 8, Hayashi does not disclose or suggest the recited effect based on a comparison to a second
5 subject having the recited very high TG levels who has not received the pharmaceutical
6 composition and a concurrent lipid altering therapy. With respect to Claim 19, Hayashi does not
7 disclose or suggest a method that is effective to reduce the recited very high TG levels without
8 substantially increasing LDL-C in a first patient population with the recited very high TG levels
9 receiving the recited dosage of the recited pharmaceutical composition without concurrent lipid
10 altering therapy, based on a comparison to a second patient population with the recited very high
11 TG levels who has not received the pharmaceutical composition and concurrent lipid altering
12 therapy.

13 Further, with respect to Claims 4 and 11, this reference fails to disclose or suggest the
14 subject and the second subject having the recited baseline lipid levels. With respect to Claims 5
15 and 12, this reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in
16 the subject based on a comparison to the second subject. With respect to Claims 6 and 13, the
17 reference fails to disclose or suggest the recited reduction in TG levels in the subject based on a
18 comparison to the second subject. With respect to claims 7 and 14, this reference fails to
19 disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject based on a
20 comparison to the second subject. With respect to Claims 15 and 17, this reference fails to
21 disclose or suggest the subject and second subject consume a Western diet. With respect to
22 Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical composition with
23 the recited fatty acid composition.
24

1 (6) Katayama

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

6 Defendants assert that certain cited sections of Katayama disclose or suggest elements of
7 the '728 Claims. The cited portions of Katayama do not disclose or suggest these elements at
8 least because they do not disclose or suggest administration of EPA with the recited purity to a
9 subject with the recited very high TG levels who does not receive concurrent lipid altering
10 therapy. The cited portions of Katayama further do not disclose or suggest the claimed
11 pharmaceutical composition with the recited fatty acid compositions or dosage. The cited
12 portions of Katayama further do not disclose or suggest a method to effect the recited TG
13 reduction without substantially increasing LDL-C.

14 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
15 Katayama does not disclose or suggest a subject with the recited very high TG levels who does
16 not receive concurrent lipid altering therapy. Katayama also does not disclose or suggest the
17 claimed pharmaceutical composition with the recited fatty acid compositions or administration
18 period. Katayama further does not disclose or suggest a method to effect the recited TG
19 reduction without substantially increasing LDL-C. Further, with respect to Claims 1 and 8,
20 Katayama does not disclose or suggest the recited effect based on a comparison to a second
21 subject having the recited very high TG levels who has not received the pharmaceutical
22 composition and a concurrent lipid altering therapy. With respect to Claim 19, Katayama does
23 not disclose or suggest a method that is effective to reduce the recited very high TG levels
24 without substantially increasing LDL-C in a first patient population with the recited very high

1 TG levels receiving the recited dosage of the recited pharmaceutical composition without
2 concurrent lipid altering therapy, based on a comparison to a second patient population with the
3 recited very high TG levels who has not received the pharmaceutical composition and concurrent
4 lipid altering therapy.

5 Further, with respect to Claims 4 and 11, this reference fails to disclose or suggest the
6 subject and the second subject having the recited baseline lipid levels. With respect to Claims 5
7 and 12, this reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in
8 the subject based on a comparison to the second subject. With respect to Claims 6 and 13, the
9 reference fails to disclose or suggest the recited reduction in TG levels in the subject based on a
10 comparison to the second subject. With respect to claims 7 and 14, this reference fails to
11 disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject based on a
12 comparison to the second subject. With respect to Claims 15 and 17, this reference fails to
13 disclose or suggest the subject and second subject consume a Western diet. With respect to
14 Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical composition with
15 the recited fatty acid composition.

16 (7) Leigh-Firbank

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

20 Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest
21 elements of the '728 Claims. The cited portions of Leigh-Firbank do not disclose or suggest
22 these elements at least because they do not disclose or suggest administration of EPA with the
23 recited purity to a subject with the recited very high TG levels who does not receive concurrent
24 lipid altering therapy. The cited portions of Leigh-Firbank further do not disclose or suggest the

1 | claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
2 | administration period. The cited portions of Leigh-Firbank further do not disclose or suggest a
3 | method to effect the recited TG reduction without substantially increasing LDL-C.

4 | With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
5 | Leigh-Firbank does not disclose or suggest a subject with the recited very high TG levels who
6 | does not receive concurrent lipid altering therapy. Leigh-Firbank also does not disclose or
7 | suggest the claimed pharmaceutical composition with the recited fatty acid compositions,
8 | dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method to
9 | effect the recited TG reduction without substantially increasing LDL-C. Further, with respect to
10 | Claims 1 and 8, Leigh-Firbank does not disclose or suggest the recited effect based on a
11 | comparison to a second subject having the recited very high TG levels who has not received the
12 | pharmaceutical composition and a concurrent lipid altering therapy. With respect to Claim 19,
13 | Leigh-Firbank does not disclose or suggest a method that is effective to reduce the recited very
14 | high TG levels without substantially increasing LDL-C in a first patient population with the
15 | recited very high TG levels receiving the recited dosage of the recited pharmaceutical
16 | composition without concurrent lipid altering therapy, based on a comparison to a second patient
17 | population with the recited very high TG levels who has not received the pharmaceutical
18 | composition and concurrent lipid altering therapy.

19 | Further, with respect to Claims 2 and 9, this reference does not disclose or suggest
20 | administration to the subject 1 to 4 times per day. With respect to Claims 4 and 11, this
21 | reference fails to disclose or suggest the subject and the second subject having the recited
22 | baseline lipid levels. With respect to Claims 5 and 12, this reference fails to disclose or suggest
23 | the recited non-HDL-C and VLDL-C effects in the subject based on a comparison to the second
24 |

1 subject. With respect to Claims 6 and 13, this reference fails to disclose or suggest the recited
2 reduction in TG in the subject based on a comparison to the second subject. With respect to
3 claims 7 and 14, this reference fails to disclose or suggest the recited reduction in fasting Lp-
4 PLA2 in the subject based on a comparison to the second subject. With respect to Claims 15 and
5 17, this reference fails to disclose or suggest the subject and second subject consume a Western
6 diet. With respect to Claims 16 and 18, this reference fails to disclose or suggest the
7 pharmaceutical composition with the recited fatty acid composition.

8 (8) Lovaza PDR

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

10 Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest
11 elements of the '728 Claims. The cited portions of the Lovaza PDR do not disclose or suggest
12 these elements at least because they do not disclose or suggest administration of EPA with the
13 recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza
14 PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited
15 fatty acid compositions or administration period. The cited portions of the Lovaza PDR further
16 do not disclose or suggest a method to effect the recited TG reduction without substantially
17 increasing LDL-C.

18 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
19 the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the
20 recited fatty acid compositions or administration period. The Lovaza PDR further does not
21 disclose or suggest a method to effect the recited TG reduction without substantially increasing
22 LDL-C. With respect to Claim 19, the Lovaza PDR does not disclose or suggest a method that is
23 effective to reduce the recited very high TG levels without substantially increasing LDL-C in a
24 first patient population with the recited very high TG levels receiving the recited dosage of the

1 recited pharmaceutical composition without concurrent lipid altering therapy, based on a
2 comparison to a second patient population with the recited very high TG levels who has not
3 received the pharmaceutical composition and concurrent lipid altering therapy.

4 Further, with respect to claims 7 and 14, this reference fails to disclose or suggest the
5 recited reduction in fasting Lp-PLA2 in the subject based on a comparison to the second subject.
6 With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject and
7 second subject consume a Western diet. With respect to Claims 16 and 18, this reference fails to
8 disclose or suggest the pharmaceutical composition with the recited fatty acid composition.

9 (9) Maki

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

12 Defendants assert that certain cited sections of Maki disclose or suggest elements of the
13 '728 Claims. The cited portions of Maki do not disclose or suggest these elements at least
14 because they do not disclose or suggest administration of EPA with the recited purity to a subject
15 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
16 cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition
17 with the recited fatty acid compositions, dosage, or administration period. The cited portions of
18 Maki further do not disclose or suggest a method of administering the claimed pharmaceutical
19 composition to effect the recited TG reduction without substantially increasing LDL-C.

20 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
21 Maki does not disclose or suggest a subject with the recited very high TG levels who does not
22 receive concurrent lipid altering therapy. Maki also does not disclose or suggest the claimed
23 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
24 period. Maki further does not disclose or suggest a method of administering the claimed

1 pharmaceutical composition to effect the recited TG reduction without substantially increasing
2 LDL-C. Further, with respect to Claims 1 and 8, Maki does not disclose or suggest the recited
3 effect based on a comparison to a second subject having the recited very high TG levels who has
4 not received the claimed pharmaceutical composition and a concurrent lipid altering therapy.

5 With respect to Claim 19, Maki does not disclose or suggest a method that is effective to reduce
6 the recited very high TG levels without substantially increasing LDL-C in a first patient
7 population with the recited very high TG levels receiving the recited dosage of the claimed
8 pharmaceutical composition without concurrent lipid altering therapy, based on a comparison to
9 a second patient population with the recited very high TG levels who has not received the
10 claimed pharmaceutical composition and concurrent lipid altering therapy.

11 With respect to Claims 2 and 9, this reference does not disclose or suggest administration
12 of the claimed pharmaceutical composition to the subject 1 to 4 times per day. With respect to
13 Claims 5 and 12, this reference fails to disclose or suggest administration of the claimed
14 pharmaceutical composition to effect the recited non-HDL-C and VLDL-C effects in the subject
15 based on a comparison to the second subject. With respect to Claims 6 and 13, this reference
16 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
17 effect the recited reduction in TG in the subject based on a comparison to the second subject.

18 With respect to Claims 7 and 14, this reference fails to disclose or suggest administration of the
19 claimed pharmaceutical composition to effect the recited reduction in fasting Lp-PLA2 in the
20 subject based on a comparison to the second subject. With respect to Claims 15 and 17, this
21 reference fails to disclose or suggest the subject and second subject consume a Western diet.

22 With respect to Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical
23 composition with the recited fatty acid composition.

24

1 (10) Matsuzawa

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

4 Defendants assert that certain cited sections of Matsuzawa disclose or suggest elements
5 of the '728 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements
6 at least because they do not disclose or suggest administration of EPA with the recited purity to a
7 subject with the recited very high TG levels who does not receive concurrent lipid altering
8 therapy. The cited portions of Matsuzawa further do not disclose or suggest these elements
9 because they do not disclose or suggest the claimed pharmaceutical composition with the recited
10 fatty acid compositions or dosage. The cited portions of Matsuzawa further do not disclose or
11 suggest a method of administering the claimed pharmaceutical composition to effect the recited
12 TG reduction without substantially increasing LDL-C.

13 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
14 Matsuzawa does not disclose or suggest the claimed pharmaceutical composition with the recited
15 fatty acid compositions or dosage. Matsuzawa further does not disclose or suggest a method of
16 administering the claimed pharmaceutical composition to effect the recited TG reduction without
17 substantially increasing LDL-C. Further, with respect to Claims 1 and 8, Matsuzawa does not
18 disclose or suggest the recited effect based on a comparison to a second subject having the
19 recited very high TG levels who has not received the pharmaceutical composition and a
20 concurrent lipid altering therapy. With respect to Claim 19, Matsuzawa does not disclose or
21 suggest a method that is effective to reduce the recited very high TG levels without substantially
22 increasing LDL-C in a first patient population with the recited very high TG levels receiving the
23 recited dosage of the recited pharmaceutical composition without concurrent lipid altering
24 therapy, based on a comparison to a second patient population with the recited very high TG

1 levels who has not received the pharmaceutical composition and concurrent lipid altering
2 therapy.

3 Further, with respect to Claims 4 and 11, this reference fails to disclose or suggest the
4 subject and the second subject having the recited baseline lipid levels. With respect to Claims 5
5 and 12, this reference fails to disclose or suggest the administration of the claimed
6 pharmaceutical composition to effect the recited non-HDL-C and VLDL-C effects in the subject
7 based on a comparison to the second subject. With respect to Claims 6 and 13, this reference
8 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
9 effect the recited reduction in TG in the subject based on a comparison to the second subject.
10 With respect to claims 7 and 14, this reference fails to disclose or suggest the administration of
11 the claimed pharmaceutical composition to effect the recited reduction in fasting Lp-PLA2 in the
12 subject based on a comparison to the second subject. With respect to Claims 15 and 17, this
13 reference fails to disclose or suggest the subject and second subject consume a Western diet.
14 With respect to Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical
15 composition with the recited fatty acid composition.

16 (11) Mori 2000

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

19 Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of
20 the '728 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at
21 least because they do not disclose or suggest administration of EPA with the recited purity to a
22 subject with the recited very high TG levels who does not receive concurrent lipid altering
23 therapy. The cited portions of Mori 2000 further do not disclose or suggest the claimed
24 pharmaceutical composition with the recited fatty acid compositions or administration period.

1 The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited
2 TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels
3 based on a comparison to a second subject with the claimed TG levels who has not received the
4 claimed pharmaceutical composition and a concurrent lipid altering therapy.

5 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
6 Mori 2000 does not disclose or suggest a subject with the recited very high TG levels who does
7 not receive concurrent lipid altering therapy. Mori 2000 further does not disclose or suggest the
8 claimed pharmaceutical composition with the recited fatty acid compositions or administration
9 period. With respect to Claims 1 and 8, Mori 200 does not disclose or suggest a method to effect
10 the recited TG reduction without substantially increasing LDL-C in the subject with the claimed
11 TG levels based on a comparison to a second subject with the claimed TG levels who has not
12 received the claimed pharmaceutical composition and a concurrent lipid altering therapy. With
13 respect to Claim 19, Mori 2000 does not disclose or suggest a method that is effective to reduce
14 the recited very high TG levels without substantially increasing LDL-C in a first patient
15 population with the recited very high TG levels receiving the recited dosage of the recited
16 pharmaceutical composition without concurrent lipid altering therapy, based on a comparison to
17 a second patient population with the recited very high TG levels who has not received the
18 pharmaceutical composition and concurrent lipid altering therapy.

19 Further, with respect to Claims 2 and 9, this reference does not disclose or suggest
20 administration to the subject 1 to 4 times per day. With respect to Claims 5 and 12, this
21 reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in the subject
22 with the claimed TG levels based on a comparison to the second subject. With respect to Claims
23 6 and 13, the reference fails to disclose or suggest the recited reduction in TG levels in the
24

1 subject with the claimed TG levels based on a comparison to the second subject. With respect to
2 claims 7 and 14, this reference fails to disclose or suggest the recited reduction in fasting Lp-
3 PLA2 in the subject with the claimed TG levels based on a comparison to the second subject.
4 With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject and
5 second subject consume a Western diet. With respect to Claims 16 and 18, this reference fails to
6 disclose or suggest the pharmaceutical composition with the recited fatty acid composition.

7 (12) Mori 2006

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

10 Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of
11 the '728 Claims. The cited portions of Mori 2006 do not disclose or suggest these elements at
12 least because they do not disclose or suggest administration of EPA with the recited purity to a
13 subject with the recited very high TG levels who does not receive concurrent lipid altering
14 therapy. The cited portions of Mori 2006 further do not disclose or suggest administration of the
15 claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
16 administration period to a subject with the claimed TG level. The cited portions of Mori 2006
17 further do not disclose or suggest a method to effect the recited TG reduction without
18 substantially increasing LDL-C in a subject with the claimed TG level.

19 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
20 Mori 2006 does not disclose or suggest a subject with the recited very high TG levels who does
21 not receive concurrent lipid altering therapy. Mori 2006 also does not disclose or suggest
22 administration of the claimed pharmaceutical composition with the recited fatty acid
23 compositions, dosage, or administration period to a subject with the claimed TG level. Mori
24 2006 further does not disclose or suggest a method to effect the recited TG reduction without

1 substantially increasing LDL-C in a subject with the claimed TG level. Further, with respect to
2 Claims 1 and 8, Mori 2006 does not disclose or suggest the recited effect based on a comparison
3 to a second subject having the recited very high TG levels who has not received the
4 pharmaceutical composition and a concurrent lipid altering therapy. With respect to Claim 19,
5 Mori 2006 does not disclose or suggest a method that is effective to reduce the recited very high
6 TG levels without substantially increasing LDL-C in a first patient population with the recited
7 very high TG levels receiving the recited dosage of the recited pharmaceutical composition
8 without concurrent lipid altering therapy, based on a comparison to a second patient population
9 with the recited very high TG levels who has not received the pharmaceutical composition and
10 concurrent lipid altering therapy.

11 Further, with respect to Claims 2 and 9, this reference does not disclose or suggest
12 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 11, this
13 reference fails to disclose or suggest the subject and the second subject having the recited
14 baseline lipid levels. With respect to Claims 5 and 12, this reference fails to disclose or suggest
15 the recited non-HDL-C and VLDL-C effects in the subject based on a comparison to the second
16 subject. With respect to Claims 6 and 13, this reference fails to disclose or suggest the recited
17 reduction in TG in the subject based on a comparison to the second subject. With respect to
18 Claims 7 and 14, this reference fails to disclose or suggest the recited reduction in fasting Lp-
19 PLA2 in the subject based on a comparison to the second subject. With respect to Claims 15 and
20 17, this reference fails to disclose or suggest the subject and second subject consume a Western
21 diet. With respect to Claims 16 and 18, this reference fails to disclose or suggest the
22 pharmaceutical composition with the recited fatty acid composition.

23 (13) Nozaki

24 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The

1 purity of the composition is reported as 90%. The study was not placebo controlled and was
2 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
3 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
4 patient population.

5 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
6 ‘728 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
7 administration of EPA with the recited purity to a subject with the recited very high TG levels
8 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
9 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
10 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
11 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
12 with the recited very high TG levels.

13 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
14 ‘728 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
15 because they do not disclose or suggest administration of EPA with the recited purity to a subject
16 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
17 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
18 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
19 further do not disclose or suggest a method to effect the recited TG reduction without
20 substantially increasing LDL-C.

21 With respect to Claims 1, 8 and 19 of the ‘728 Patent (and therefore all asserted claims),
22 Nozaki does not disclose or suggest a subject with the recited very high TG levels who does not
23 receive concurrent lipid altering therapy. Nozaki also does not disclose or suggest the claimed
24

1 pharmaceutical composition with the recited fatty acid compositions or administration period.
2 Nozaki further does not disclose or suggest a method to effect the recited TG reduction without
3 substantially increasing LDL-C. Further, with respect to Claims 1 and 8, Nozaki does not
4 disclose or suggest the recited effect based on a comparison to a second subject having the
5 recited very high TG levels who has not received the pharmaceutical composition and a
6 concurrent lipid altering therapy. With respect to Claim 19, Nozaki does not disclose or suggest
7 a method that is effective to reduce the recited very high TG levels without substantially
8 increasing LDL-C in a first patient population with the recited very high TG levels receiving the
9 recited dosage of the recited pharmaceutical composition without concurrent lipid altering
10 therapy, based on a comparison to a second patient population with the recited very high TG
11 levels who has not received the pharmaceutical composition and concurrent lipid altering
12 therapy.

13 Further, with respect to Claims 4 and 11, this reference fails to disclose or suggest the
14 subject and the second subject having the recited baseline lipid levels. With respect to Claims 5
15 and 12, this reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in
16 the subject based on a comparison to the second subject. With respect to Claims 6 and 13, the
17 reference fails to disclose or suggest the recited reduction in TG levels in the subject based on a
18 comparison to the second subject. With respect to claims 7 and 14, this reference fails to
19 disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject based on a
20 comparison to the second subject. With respect to Claims 15 and 17, this reference fails to
21 disclose or suggest the subject and second subject consume a Western diet. With respect to
22 Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical composition with
23 the recited fatty acid composition.

24

1 (14) Omacor PDR

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

3 Defendants assert that certain cited sections of the Omacor PDR disclose or suggest
4 elements of the '728 Claims. The cited portions of the Omacor PDR do not disclose or suggest
5 these elements at least because they do not disclose or suggest administration of EPA with the
6 recited purity to a subject with the recited very high TG levels. The cited portions of the Omacor
7 PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited
8 fatty acid compositions or administration period. The cited portions of the Omacor PDR further
9 do not disclose or suggest a method to effect the recited TG reduction without substantially
10 increasing LDL-C.

11 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
12 the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the
13 recited fatty acid compositions or administration period. The Omacor PDR further does not
14 disclose or suggest a method to effect the recited TG reduction without substantially increasing
15 LDL-C. With respect to Claim 19, the Omacor PDR does not disclose or suggest a method that
16 is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a
17 first patient population with the recited very high TG levels receiving the recited dosage of the
18 recited pharmaceutical composition without concurrent lipid altering therapy, based on a
19 comparison to a second patient population with the recited very high TG levels who has not
20 received the pharmaceutical composition and concurrent lipid altering therapy.

21 Further, with respect to claims 7 and 14, this reference fails to disclose or suggest the
22 recited reduction in fasting Lp-PLA2 in the subject based on a comparison to the second subject.
23 With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject and
24

1 second subject consume a Western diet. With respect to Claims 16 and 18, this reference fails to
2 disclose or suggest the pharmaceutical composition with the recited fatty acid composition.

3 (15) Satoh

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

7 Defendants assert that certain cited sections of Satoh disclose or suggest elements of the
8 '728 Claims. The cited portions of Satoh do not disclose or suggest these elements at least
9 because they do not disclose or suggest administration of EPA with the recited purity to a subject
10 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
11 cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical
12 composition with the recited fatty acid compositions or dosage. The cited portions of Satoh
13 further do not disclose or suggest a method to effect the recited TG reduction without
14 substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison
15 to a second subject with the claimed TG levels who has not received the claimed pharmaceutical
16 composition and a concurrent lipid altering therapy.

17 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
18 Satoh does not disclose or suggest a subject with the recited very high TG levels who does not
19 receive concurrent lipid altering therapy. Satoh further does not disclose or suggest the claimed
20 pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to
21 Claims 1 and 8, Satoh does not disclose or suggest a method to effect the recited TG reduction
22 without substantially increasing LDL-C in the subject with the claimed TG levels based on a
23 comparison to a second subject with the claimed TG levels who has not received the claimed
24 pharmaceutical composition and a concurrent lipid altering therapy. With respect to Claim 19,

1 | Satoh does not disclose or suggest a method that is effective to reduce the recited very high TG
2 | levels without substantially increasing LDL-C in a first patient population with the recited very
3 | high TG levels receiving the recited dosage of the recited pharmaceutical composition without
4 | concurrent lipid altering therapy, based on a comparison to a second patient population with the
5 | recited very high TG levels who has not received the pharmaceutical composition and concurrent
6 | lipid altering therapy.

7 | Further, with respect to Claims 5 and 12, this reference fails to disclose or suggest the
8 | recited non-HDL-C and VLDL-C effects in the subject with the claimed TG levels based on a
9 | comparison to the second subject. With respect to Claims 6 and 13, the reference fails to
10 | disclose or suggest the recited reduction in TG levels in the subject with the claimed TG levels
11 | based on a comparison to the second subject. With respect to claims 7 and 14, this reference
12 | fails to disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject with the
13 | claimed TG levels based on a comparison to the second subject. With respect to Claims 15 and
14 | 17, this reference fails to disclose or suggest the subject and second subject consume a Western
15 | diet. With respect to Claims 16 and 18, this reference fails to disclose or suggest the
16 | pharmaceutical composition with the recited fatty acid composition.

17 | (16) Shinozaki

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

20 | Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of
21 | the '728 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at
22 | least because they do not disclose or suggest administration of EPA with the recited purity to a
23 | subject with the recited very high TG levels who does not receive concurrent lipid altering
24 | therapy. The cited portions of Shinozaki further do not disclose or suggest the claimed

1 pharmaceutical composition with the recited fatty acid dosage. The cited portions of Shinozaki
2 further do not disclose or suggest a method to effect the recited TG reduction without
3 substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison
4 to a second subject with the claimed TG levels who has not received the claimed pharmaceutical
5 composition and a concurrent lipid altering therapy.

6 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
7 Shinozaki does not disclose or suggest a subject with the recited very high TG levels who does
8 not receive concurrent lipid altering therapy. Shinozaki further does not disclose or suggest the
9 claimed pharmaceutical composition with the recited fatty acid dosage. With respect to Claims 1
10 and 8, Shinozaki does not disclose or suggest a method to effect the recited TG reduction without
11 substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison
12 to a second subject with the claimed TG levels who has not received the claimed pharmaceutical
13 composition and a concurrent lipid altering therapy. With respect to Claim 19, Shinozaki does
14 not disclose or suggest a method that is effective to reduce the recited very high TG levels
15 without substantially increasing LDL-C in a first patient population with the recited very high
16 TG levels receiving the recited dosage of the recited pharmaceutical composition without
17 concurrent lipid altering therapy, based on a comparison to a second patient population with the
18 recited very high TG levels who has not received the pharmaceutical composition and concurrent
19 lipid altering therapy.

20 Further, with respect to Claims 2 and 9, this reference does not disclose or suggest
21 administration to the subject 1 to 4 times per day. With respect to Claims 4 and 11, this
22 reference fails to disclose or suggest the subject and the second subject having the recited
23 baseline lipid levels. With respect to Claims 5 and 12, this reference fails to disclose or suggest
24

1 the recited non-HDL-C and VLDL-C effects in the subject with the claimed TG levels based on a
2 comparison to the second subject. With respect to Claims 6 and 13, the reference fails to
3 disclose or suggest the recited reduction in TG levels in the subject with the claimed TG levels
4 based on a comparison to the second subject. With respect to claims 7 and 14, this reference
5 fails to disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject with the
6 claimed TG levels based on a comparison to the second subject. With respect to Claims 15 and
7 17, this reference fails to disclose or suggest the subject and second subject consume a Western
8 diet. With respect to Claims 16 and 18, this reference fails to disclose or suggest the
9 pharmaceutical composition with the recited fatty acid composition.

10 (17) Takaku

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

13 Defendants assert that certain cited sections of Takaku disclose or suggest elements of the
14 '728 Claims. The cited portions of Takaku do not disclose or suggest these elements at least
15 because they do not disclose or suggest administration of EPA with the recited purity to a subject
16 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
17 cited portions of Takaku further do not disclose or suggest these elements because they do not
18 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
19 compositions or dosage. The cited portions of Takaku further do not disclose or suggest a
20 method of administering the claimed pharmaceutical composition to effect the recited TG
21 reduction without substantially increasing LDL-C.

22 With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims),
23 Takaku does not disclose or suggest the claimed pharmaceutical composition with the recited
24 fatty acid compositions or dosage. Takaku further does not disclose or suggest a method of

1 administering the claimed pharmaceutical composition to effect the recited TG reduction without
2 substantially increasing LDL-C. Further, with respect to Claims 1 and 8, Takaku does not
3 disclose or suggest the recited effect based on a comparison to a second subject having the
4 recited very high TG levels who has not received the pharmaceutical composition and a
5 concurrent lipid altering therapy. With respect to Claim 19, Takaku does not disclose or suggest
6 a method that is effective to reduce the recited very high TG levels without substantially
7 increasing LDL-C in a first patient population with the recited very high TG levels receiving the
8 recited dosage of the recited pharmaceutical composition without concurrent lipid altering
9 therapy, based on a comparison to a second patient population with the recited very high TG
10 levels who has not received the pharmaceutical composition and concurrent lipid altering
11 therapy.

12 Further, with respect to Claims 4 and 11, this reference fails to disclose or suggest the
13 subject and the second subject having the recited baseline lipid levels. With respect to Claims 5
14 and 12, this reference fails to disclose or suggest the recited non-HDL-C and VLDL-C effects in
15 the subject with the claimed TG levels based on a comparison to the second subject. With
16 respect to Claims 6 and 13, the reference fails to disclose or suggest the recited reduction in TG
17 levels in the subject with the claimed TG levels based on a comparison to the second subject.
18 With respect to claims 7 and 14, this reference fails to disclose or suggest the recited reduction in
19 fasting Lp-PLA2 in the subject with the claimed TG levels based on a comparison to the second
20 subject. With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject
21 and second subject consume a Western diet. With respect to Claims 16 and 18, this reference
22 fails to disclose or suggest the pharmaceutical composition with the recited fatty acid
23 composition.

24

1 c) The Prior Art Does Not Render the Claims Obvious

2 Defendants have not identified by clear and convincing evidence that the asserted claims
3 of the '728 Patent would have been *prima facie* obvious in light of the references cited, either
4 alone or in combination. As described above, none of the references discloses all of the elements
5 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
6 explanation, and argue they somehow must be combined to render obvious the asserted claims.
7 Where Defendants have failed to make disclosures with the specificity required by Local Patent
8 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
9 claim elements at issue.

10 Defendants' contentions fail to disclose each and every element of the claims of the '728
11 patent. Specifically, Defendants do not contend that the relied upon references disclose the
12 following elements of Claim 1 (and therefore Claims 2-7, 15 and 16): (1) a subject having a
13 fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl *who does not receive*
14 *concurrent lipid altering therapy*; or (2) administering the claimed pharmaceutical composition
15 to the recited subject to effect a reduction in triglycerides without substantially increasing LDL-
16 C based on a comparison to a second subject having a fasting baseline triglyceride level of 500
17 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a
18 concurrent lipid altering therapy.

19 In addition, Defendants do not contend that the relied upon references disclose the
20 following elements of Claim 8 (and therefore Claims 9-14,17 and 18): (1) a subject having a
21 fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl *who does not receive*
22 *concurrent lipid altering therapy*; or (2) administering a pharmaceutical composition to the
23 recited subject to effect a reduction in fasting triglycerides of at least about 15% without
24 substantially increasing LDL-C in the subject based upon a comparison to a second subject

1 having fasting triglyceride of 500 mg/dl to about 1500 who has not received the pharmaceutical
2 composition and concurrent lipid altering therapy.

3 Further, Defendants do not contend that the relied upon references disclose the following
4 elements of Claim 19: (1) a subject having a fasting baseline triglyceride level of about 500
5 mg/dl to about 1500 mg/dl, *who does not receive a concurrent lipid altering therapy*; (2)
6 administering a pharmaceutical composition that is effective to reduce in a first patient
7 population receiving 4 g per day of said composition without concurrent lipid altering therapy
8 and having said baseline triglyceride level, a median triglyceride level by at least 5% without
9 substantially increasing LDL-C, compared to a median triglyceride level and LDL-C level
10 observed in a second patient population having said baseline triglyceride level who has not
11 received the pharmaceutical composition and concurrent lipid altering therapy.

12 Therefore, Defendants' prior art combinations cannot render the claims *prima facie*
13 obvious.

14 Facts supporting the non-obviousness of the claims of the '728 patent are discussed in
15 detail below. The objective indicia discussed in Section V.O further demonstrate that the '728
16 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims
17 would have been obvious.

18 (1) Defendants Do Not Demonstrate that the Independent
19 Claims of the '728 Patent Would Have Been Obvious

20 (a) Defendants Do Not Demonstrate that a Person of
21 Ordinary Skill in the Art Would Have Had Any
22 Reason to Replace the Mixed Fish Oil Active
23 Ingredient in Lovaza with Pure EPA

24 (i) The '728 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

(and/or Satoh or Shinozaki in view of Contacos)

With respect to the '728 Patent, Defendants present a combination of ten 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 (and/or Satoh or Shinozaki in view of Contacos).”⁵⁸⁷ 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.^{588 589} 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.⁵⁹⁰ Defendants’ unsupported cobbling of selective disclosures represents hindsight

⁵⁸⁷ Defendants’ Joint Invalidity Contentions at 205-06.

⁵⁸⁸ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as described in the references cited above in section V.B.2 in view of, at least, the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matak, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity Contentions at 205.

⁵⁸⁹ 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 203-204.

⁵⁹⁰ *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.”); *Daichi*

1 reconstruction.⁵⁹¹ Defendants’ contentions are no more than an assertion that certain claim
2 elements were known in the prior art. Throughout their contentions, Defendants selectively cite
3 to data points in a reference without considering other disclosures or even the reference as a
4 whole. Each reference, however, must be evaluated for all that it teaches.⁵⁹² Accordingly,
5 Defendants fail to meet their burden to establish *prima facie* obviousness.

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

15 The proposed combinations do not render the independent claims of the ’728 Patent
16 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO

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Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 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).

⁵⁹¹ See, e.g., *Immogenetics 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”).

⁵⁹² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
2 package insert specifically) during prosecution.⁵⁹³

3 With respect to Claims 8 and 19, Defendants contend, without support, that “[a]s there is
4 no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been
5 obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without
6 increasing LDL-C, in this manner, with a reasonable expectation of success.” Defendants further
7 contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the
8 recited amount because there is no significance attached to the amount. Defendants conclude,
9 without support, that there was a reasonable expectation of success without identifying any
10 combination of references and without explaining how each reference relates to the claimed
11 invention.⁵⁹⁴ These contentions are inadequate to establish *prima facie* obviousness.

12 Because Defendants do not identify any combination of references, they necessarily fail
13 to offer any evidence that a person of skill in the art would be motivated to combine those
14 references in order to achieve the invention of the claim as a whole. Defendants make a
15 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
16 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
17 person of ordinary skill to reduce triglycerides by the recited amount.⁵⁹⁵ Defendants’ burden to
18

19 ⁵⁹³ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
20 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”).

21 ⁵⁹⁴ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris-Etherton 2002, Kurabayashi, Leigh-
22 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.

23 ⁵⁹⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
24 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning

1 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
2 attached to the recited TG reduction amount.⁵⁹⁶ Defendants have not met the burden with the
3 naked assertion that it would have been obvious to seek the claim element.

4 Similarly, without the disclosure of a combination of references and a motivation/reason
5 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
6 person of ordinary skill in the art would have had a reasonable expectation of success in
7 achieving the claimed invention. Defendants make a conclusory statement that there was a
8 reasonable expectation of success, without providing a support other than merely identifying
9 prior art references that purportedly disclose disparate elements.⁵⁹⁷ The mere fact that elements
10 are capable of being physically combined does not establish reasonable expectation of success.⁵⁹⁸

11 Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting
12 TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively.
13 Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per
14

15 _____
16 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
17 quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir.
18 2007) (“While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in
19 an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a
20 person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in
21 an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

22 ⁵⁹⁶ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
23 established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
24 case of obviousness by establishing that the claimed range is critical”) (internal quotation marks omitted).

⁵⁹⁷ *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).

⁵⁹⁸ *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.”).

1 day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.⁵⁹⁹
2 Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient*
3 *population*, and does not provide any reasonable expectation of success in lowering TG levels in
4 the very high TG patient population without increasing LDL-C. Defendants discuss the claim
5 elements in isolation, and fail to address the claimed invention as a whole.⁶⁰⁰ Defendants
6 selectively cite to an unspecified isolated disclosure within a reference without considering other
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
8 that it teaches.⁶⁰¹ Defendants’ unsupported cobbling of selective disclosures represents hindsight
9 reconstruction.⁶⁰²

10 The analysis of the independent claims of the ’728 Patent is incorporated into all asserted
11 claims that depend from those Claims.

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

15 For an invention to be obvious, there must have been an “apparent reason” to make it.
16 The subject matter of the ‘728 patent claims would not have been obvious in light of these
17 references because a person of ordinary skill would not have been motivated to purify EPA or
18 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
19 levels without an increase in LDL-C levels.

20 ⁵⁹⁹ See Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

21 ⁶⁰⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
22 made with respect to the subject matter as a whole, not separate pieces of the claim”).

23 ⁶⁰¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁶⁰² 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”).

(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.⁶⁰³ 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 ‘728 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

⁶⁰³See 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.)

1 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
2 lowering through increased VLDL particle conversion.

3 Defendants argue that these studies disclose known “clinical benefits” of administering
4 pure EPA, lowering triglycerides without raising LDL-C.⁶⁰⁴ This is an incorrect characterization
5 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
6 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
7 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
8 Defendants’ selective citation of LDL-C data from these references represents the improper use
9 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
10 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
11 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
12 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
13 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.⁶⁰⁵ The
14 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
15 would a person of ordinary skill view these references as teaching such a benefit for very-high
16 TG patients.

17 Further, both Katayama and Matsuzawa administered only EPA and studied its lipid
18 effects. These studies fail to provide a head to head comparison of EPA versus DHA.
19 Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to
20 draw any conclusions related to possible differences between the lipid effects of EPA and DHA.
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23 ⁶⁰⁴ Defendants’ Joint Invalidation Contentions at 206.

24 ⁶⁰⁵ Defendants’ Joint Invalidation Contentions at 206.

1 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
2 purity of Epadel has varied over time and across different formulations of the product, therefore
3 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
4 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
5 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
6 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
7 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.
8 Nishikawa,⁶⁰⁶ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
9 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
10 purity.⁶⁰⁷

11 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
12 patients. These studies would not have been extrapolated to Western populations because the
13 Japanese diet contains much more fish and has a number of other different attributes. The
14 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
15 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
16 the patient population is exclusively Japanese cannot be generalized to other populations.⁶⁰⁸ The
17 Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western
18 Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty
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21 ⁶⁰⁶ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS*
22 *Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

23 ⁶⁰⁷ See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

24 ⁶⁰⁸ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

1 acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the
2 Japanese respond differently to lipid lowering agents than Westerners.

3 Defendants rely on Katayama to demonstrate the “known clinical benefits of
4 administering pure EPA - lowering triglycerides without raising LDL-C.”⁶⁰⁹ However,
5 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
6 treatment in patients with hyperlipidemia.⁶¹⁰ Katayama does not disclose *any* LDL-C related
7 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
8 reference to provide any such disclosure. The only results disclosed by Katayama were a
9 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
10 administered to patients with borderline-high to high TG levels, and its safety for long term use
11 in this patient population.⁶¹¹ In addition to Katayama’s lack of disclosure regarding LDL-C,
12 Defendants identify no other basis upon which a person of ordinary skill would have sought to
13 combine the composition disclosed in Katayama with the Lovaza PDR.

14 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
15 administering pure EPA - lowering triglycerides without raising LDL-C.”⁶¹² However,
16 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
17 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
18 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
19 were evaluated for improvement in serum triglycerides levels.⁶¹³ It is unclear which of the 26
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21 ⁶⁰⁹ Defendants’ Joint Invalidation Contentions at 206.

22 ⁶¹⁰ Katayama at 2.

23 ⁶¹¹ *Id.* at 16.

24 ⁶¹² Defendants’ Joint Invalidation Contentions at 206.

⁶¹³ Matsuzawa at 7 and 19.

1 patients were included in each separate evaluation; therefore one cannot determine the baseline
2 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
3 of a placebo control makes it less likely that the results of this study can be generalized as an
4 effect on any population as a whole and provides no insight with respect to the very-high TG
5 patient population.

6 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
7 and one participant with TG levels > 1,000 mg/dL.⁶¹⁴ However, when analyzing the lipid impact
8 of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he
9 was a “heavy drinker” and the “effect of alcohol made it impossible to assess triglyceride
10 levels.”⁶¹⁵ Fig. 4, which depicts the changes in serum triglycerides, shows that the mean
11 triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL.
12 Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the
13 excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
14 undisclosed purity). The identification of three patients with TG levels between 400 and less
15 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dL, and a person of
16 ordinary skill would not understand that the reference makes any such disclosure. As discussed
17 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
18 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
19 evidence to the contrary.

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23 ⁶¹⁴ *Id.* at 23.

24 ⁶¹⁵ *Id.* at 10.

1 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
2 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.⁶¹⁶ The disclosure
3 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
4 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
5 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
6 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
7 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
8 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
9 skill in the art, however, would have expected the same treatment in patients with very high TG
10 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
11 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
12 triglyceride levels.⁶¹⁷ At best, Matsuzawa demonstrates the uncertainty and confusion related to
13 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
14 any other basis upon which a person of ordinary skill would have sought to combine the
15 composition disclosed in Matsuzawa with the Lovaza PDR.

16 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
17 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
18 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
19 increases LDL-C.⁶¹⁸ Defendants identify no other basis upon which a person of ordinary skill
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⁶¹⁶ *Id.* at 11.

22 ⁶¹⁷ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
24 compositions used, or identify the patient populations were observed.

⁶¹⁸ *See, e.g.,* Rambjor.

1 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
2 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
3 asserted claims of the '728 patent.

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

7 Defendants contend that the asserted claims of the '728 patent would have been obvious
8 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
9 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
10 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
11 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
12 very high TG patient population.

13 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
14 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
15 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
16 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
17 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
18 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
19 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
20 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
21 patient population were abnormally high and would not have relied upon these results. Further,
22 the person of skill in the art would not have looked to this patient population to predict the Apo-
23 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
24 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol

1 levels.⁶¹⁹ Nozaki does not provide a motivation or reasonable expectation of success for
2 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
3 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
4 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
5 to the very high TG patient population.

6 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
7 the EPA and the DHA content in the composition that was administered is unknown. A person
8 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
9 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
10 C were not statistically significant.⁶²⁰ Further, the person of skill in the art would not have
11 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
12 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
13 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
14 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
15 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
16 administered to the very high TG patient population.

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

22 _____
23 ⁶¹⁹ Nozaki at 256.

24 ⁶²⁰ Hayashi at 26, Table I.

1 patient population is exclusively Japanese cannot be generalized to other populations.⁶²¹ The
2 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
3 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
4 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
5 the Japanese respond differently to lipid lowering agents than Westerners.

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

11 (iii) Leigh-Firbank and/or Mori
12 2000 (and/or Satoh or
13 Shinozaki in view of
14 Contacos) Do Not Disclose
Purported Knowledge that
DHA was Responsible for the
Increase in LDL-C

15 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
16 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
17 C levels.”⁶²² Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
18 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
19 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
20 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
21 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As

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23 ⁶²¹ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
other populations.”).

24 ⁶²² Defendants’ Joint Invalidity Contentions at 209.

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

10 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
11 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
12 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
13 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
14 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
15 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
16 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
17 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
18 acknowledges that EPA- and DHA-enriched oils, which are contained other saturated and
19 polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and
20 DHA.⁶²³ A person of ordinary skill would understand that studies directed to EPA and DHA-
21 enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid
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24 ⁶²³ Mori 2006 at 96.

1 parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
2 Firbank, because purified EPA and DHA were not administered separately.

3 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
4 effects of EPA and DHA individually, even though it administered a combination of EPA and
5 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
6 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
7 phospholipid EPA were *independently* associated with the decrease in fasting TGs,⁶²⁴ and DHA
8 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
9 of the art and numerous publications cited by Defendants.⁶²⁵ It is widely accepted that DHA also
10 has a hypotriglyceridemic effect.

11 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
12 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
13 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
14 away from the claimed invention. “A reference may be said to teach away when a person of
15 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
16 out in the reference, or would be led in a direction divergent from the path that was taken by the
17 applicant.”⁶²⁶ Although teaching away is fact-dependent, “in general, a reference will teach
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22 ⁶²⁴ Leigh-Firbank at 440.

23 ⁶²⁵ See, e.g. Grimsgaard at 654.

24 ⁶²⁶ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

1 away if it suggests that the line of development flowing from the reference’s disclosures is
2 unlikely to be productive of the result sought by the applicant.”⁶²⁷

3 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
4 a more favorable lipid profile than after EPA supplementation.”⁶²⁸ For example, it states that
5 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
6 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
7 effects on fasting glucose concentrations.”⁶²⁹ Mori 2000 also states that “[d]espite an increase in
8 LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be
9 favorable.”⁶³⁰ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori 2000,
10 a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact
11 opposite of what Defendants argue in their contentions. Therefore, the art taught away from
12 using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or
13 selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA, despite
14 disclosed advantages of DHA. A person of ordinary skill would take into consideration the
15 entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
16 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
17 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
18 would have sought to combine Mori 2000 with the Lovaza PDR.

20 ⁶²⁷ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); see also *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
21 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
22 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

22 ⁶²⁸ Mori 2000 at 1092.

23 ⁶²⁹ Mori 2000 at 1088.

24 ⁶³⁰ Mori 2000 at 1092.

1 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
2 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
3 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
4 has little effect on LDL-C levels.⁶³¹ Defendants identify no other basis upon which a person of
5 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
6 Leigh-Firbank and/or Mori 2000.

7 Defendants purport to formulate an obviousness argument that relies on Satoh or
8 Shinozaki in view of Contacos.^{632,633} However, Defendants fail to provide any factual or legal
9 basis as to why Satoh, Shinozaki, or Contacos disclose a claim element, an “apparent reason” or
10 motivation to combine the elements in the manner claimed,⁶³⁴ or “a reasonable expectation of
11 success”⁶³⁵ of achieving the claimed invention.

12 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
13 pravastatin, but it does not disclose administration of EPA of the recited composition. Contacos
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15 ⁶³¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

16 ⁶³² Defendants’ Joint Invalidity Contentions at 206.

17 ⁶³³ Further, it is not apparent what combination or combinations of references Defendants assert in their purported
18 obviousness argument based on “Omacor PDR/Lovaza PDR in combination with . . . Katayama and/or Matsuzawa,
19 further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or
20 Shinozaki in view of Contacos).” In failing to identify the role of “Satoh or Shinozaki in view of Contacos” in this
21 purported obviousness combination or offer any associated explanation, they have failed to meet their contentions
22 burden. Accordingly, defendants should be precluded from relying on this purported combination.

20 ⁶³⁴ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
23 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ⁶³⁵ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 demonstrated that fish oil does not increase LDL-C or Apo-B when administered to patients.
2 Contacos also fails to provide motivation to administer purified EPA to a very high TG patient
3 population and does not provide any reasonable expectation of success in lowering TG levels in
4 the very high TG patient population without increasing LDL-C or Apo-B.

5 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
6 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
7 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
8 compared to baseline, there was no significant effect when compared to placebo.⁶³⁶ Satoh does
9 not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a
10 person of ordinary skill view these references as teaching such a benefit for very-high TG
11 patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to
12 increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary.
13 A person of ordinary skill in the art, however, would have expected that fish oils (and other TG
14 lowering agents) would substantially increase LDL-C in patients with very high TG levels. In
15 addition, Satoh does not disclose the effect of EPA on Apo-B. Satoh fails to provide motivation
16 to administer purified EPA to a very high TG patient population and does not provide any
17 reasonable expectation of success in lowering TG levels in the very high TG patient population
18 without increasing LDL-C or Apo-B.

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

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24 ⁶³⁶ Satoh at 145.

1 states that the results from studies where the patient population is exclusively Japanese cannot be
2 generalized to other populations.⁶³⁷ The Japanese diet comprises between 8 and 15 times more
3 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
4 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
5 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
6 agents than Westerners.

7 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
8 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
9 Shinozaki says nothing about an LDL-C or Apo-B effect because it measured only LDL particle
10 number and Lp(a), and did not measure LDL-C or Apo-B. The finding disclosed by Shinozaki
11 was that “long term administration of EPA may lower Lp(a) and serum lipids.”⁶³⁸ In addition to
12 Shinozaki’s lack of disclosure regarding LDL-C or Apo-B, Defendants identify no other basis
13 upon which a person of ordinary skill would have sought to combine the composition disclosed
14 in Shinozaki.

15 Defendants identify no other basis upon which a person of ordinary skill would have
16 sought to combine the “Omacor PDR/Lovaza PDR in combination with . . . Katayama and/or
17 Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank
18 and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos).”

- 19 (ii) The ‘728 Patent is not Obvious Over the
20 Omacor PDR/Lovaza PDR, in Combination
21 with Katayama and/or Matsuzawa, and/or
Takaku, in further view of Nozaki and/or

22 _____
23 ⁶³⁷ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
other populations.”).

24 ⁶³⁸ Shinozaki at 107-109.

With respect to the '728 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, and further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki.”⁶³⁹

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.⁶⁴⁰ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁶⁴¹ Defendants’ contentions are no more than an assertion that certain claim

⁶³⁹ Defendants’ Joint Invalidity Contentions at 206.

⁶⁴⁰ 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).

⁶⁴¹ See, e.g., *Immogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 elements were known in the prior art. Throughout their contentions, Defendants’ selectively cite
2 to data points in a reference without considering other disclosures or even the reference as a
3 whole. Each reference, however, must be evaluated for all that it teaches.⁶⁴² Accordingly,
4 Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
8 further do not disclose a method to effect the claimed TG reduction without substantially
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
14 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’728
15 Patent obvious and Defendants’ burden to prove otherwise is especially difficult because the
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
17 generally and the Lovaza package insert specifically) during prosecution.⁶⁴³

18 With respect to Claims 8 and 19, Defendants contend, without support, that “[a]s there is
19 no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been
20 obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without
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22 ⁶⁴² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁶⁴³ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 increasing LDL-C, in this manner, with a reasonable expectation of success.” Defendants further
2 contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the
3 recited amount because there is no significance attached to the amount. Defendants conclude,
4 without support, that there was a reasonable expectation of success without identifying any
5 combination of references and without explaining how each reference relates to the claimed
6 invention.⁶⁴⁴ These contentions are inadequate to establish *prima facie* obviousness.

7 Because Defendants do not identify any combination of references, they necessarily fail
8 to offer any evidence that a person of skill in the art would be motivated to combine those
9 references in order to achieve the invention of the claim as a whole. Defendants make a
10 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
11 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
12 person of ordinary skill to reduce triglycerides by the recited amount.⁶⁴⁵ Defendants’ burden to
13 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
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18 ⁶⁴⁴ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris Etherton 2002, Kurabayashi, Leigh-
19 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.

20 ⁶⁴⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
21 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
22 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
23 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
24 an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a
person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in
an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 attached to the recited TG reduction amount.⁶⁴⁶ Defendants have not met the burden with the
2 naked assertion that it would have been obvious to seek the claim element.

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. Defendants make a conclusory statement that there was a
7 reasonable expectation of success, without providing a support other than merely identifying
8 prior art references that purportedly disclose disparate elements.⁶⁴⁷ The mere fact that elements
9 are capable of being physically combined does not establish reasonable expectation of success.⁶⁴⁸

10 Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting
11 TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively.
12 Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per
13 day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.⁶⁴⁹
14 Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient*
15 *population*, and does not provide any reasonable expectation of success in lowering TG levels in
16 the very high TG patient population without increasing LDL-C. Defendants discuss the claim

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18 ⁶⁴⁶ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
19 established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
20 case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

21 ⁶⁴⁷ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
22 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
23 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
24 quotation marks omitted).

⁶⁴⁸ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
22 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
23 combined, but also that the combination would have worked for its intended purpose.”).

⁶⁴⁹ See Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

1 elements in isolation, and fail to address the claimed invention as a whole.⁶⁵⁰ Defendants
2 selectively cite to an unspecified isolated disclosure within a reference without considering other
3 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
4 that it teaches.⁶⁵¹ Defendants’ unsupported cobbling of selective disclosures represents hindsight
5 reconstruction.⁶⁵²

6 The analysis of the independent claims of the ’728 Patent is incorporated into all asserted
7 claims that depend from those Claims.

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

11 For an invention to be obvious, there must have been an “apparent reason” to make it.
12 The subject matter of the ’728 patent claims would not have been obvious in light of these
13 references because a person of ordinary skill would not have been motivated to purify EPA or
14 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
15 levels without an increase in LDL-C levels.

16 (i) Grimsgaard, Katayama,
17 Matsuzawa and/or Takaku
18 Do Not Disclose Purported
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21 ⁶⁵⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
22 made with respect to the subject matter as a whole, not separate pieces of the claim”).

23 ⁶⁵¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁶⁵² *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
“[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

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

10 Defendants also rely on Grimsgaard to support their assertion that “administration of
11 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”⁶⁵³ However,
12 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
13 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

14 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
15 administered to people with normal triglyceride levels for 7 weeks.⁶⁵⁴ The results from the
16 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
17 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
18 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
19 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
20 better maintained with oil rich in DHA than oil rich in EPA.”⁶⁵⁵ Although Grimsgaard states that

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22 ⁶⁵³ Defendants’ Joint Invalidity Contentions at 209.

23 ⁶⁵⁴ Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG
24 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

⁶⁵⁵ Grimsgaard at 654.

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.”⁶⁵⁶ The results of Grimsgaard, reproduced below, show that EPA and DHA's impact on LDL-C were the same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard's disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' Joint Invalidity Contentions.

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

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	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 ³	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 ³	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 $\bar{x} \pm$ 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.”⁶⁵⁷ However, Grimsgaard does not conclude

⁶⁵⁶ Defendants' Joint Invalidity Contentions at 209 n.22.

⁶⁵⁷ Grimsgaard at 657.

1 that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that
2 neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and
3 DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading
4 Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of
5 patients with very-high triglycerides, because net decrease in triglycerides was consistently
6 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared
7 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL
8 cholesterol observed with some n-3 fatty acid supplements.”⁶⁵⁸ Grimsgaard makes no such
9 statement regarding LDL-C.

10 Defendants cherry-pick results, regardless of whether the effect is found to be statistically
11 significant compared to placebo, in an attempt to force the studies to support their argument that
12 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
13 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
14 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
15 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
16 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
17 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
18 not have statistically significantly effects on LDL-C compared to placebo.⁶⁵⁹ A person of
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21 ⁶⁵⁸ Grimsgaard at 654.

22 ⁶⁵⁹In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
23 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
24 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
no impact on LDL-C levels.

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

3 Defendants also rely on Takaku to support their assertion that “clinical benefits of
4 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
5 art.⁶⁶⁰ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
6 safety of Epadel (of undisclosed purity)⁶⁶¹ based on long-term administration.⁶⁶²

7 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
8 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
9 acknowledges that “only a few subjects were examined” and cautions against drawing a
10 conclusion “only from the results of the present study.”⁶⁶³ Because the study did not include any
11 placebo control, a person of ordinary skill in the art would understand these reports do not
12 provide the ability to conclude that the observed lipid effects would have occurred independent
13 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
14 patients, and a person of ordinary skill would not have expected the results to be applicable to the
15 general population.⁶⁶⁴

16 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
17 person of ordinary skill would not have expected the results to be applicable to patients with
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19 ⁶⁶⁰ Defendants’ Joint Invalidity Contentions at 206.

20 ⁶⁶¹ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
21 the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
Nakamura at 23 (Epadel with purity > 90%).

22 ⁶⁶² Takaku at ICOSAPENT_DFNDT00006834.

23 ⁶⁶³ Takaku at ICOSAPENT_DFNDT00006897.

24 ⁶⁶⁴ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

1 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
2 measurement was not feasible due to “insufficient sample.”⁶⁶⁵ It is possible that patients with
3 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
4 calculating LDL-C levels when triglyceride level is above 400 mg/dL.⁶⁶⁶ Moreover, the study
5 does not provide different LDL-C graphs based on the baseline triglyceride levels.⁶⁶⁷ Therefore,
6 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
7 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
8 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
9 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
10 times.⁶⁶⁸ Because of this volatility, a person of ordinary skill would not be able to conclude what
11 effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-
12 C, stating only that the fluctuation in LDL-C was not significant.⁶⁶⁹

13 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
14 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
15 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
16 administration of *fish oil* to hypercholesterolemia patients.”⁶⁷⁰ In contrast, Takaku states merely
17 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
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20 ⁶⁶⁵ Takaku at ICOSAPENT_DFNDT00006884.

21 ⁶⁶⁶ See Matsuzawa at ICOSPENT_DFNDTS00006450.

22 ⁶⁶⁷ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

23 ⁶⁶⁸ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

24 ⁶⁶⁹ Takaku at ICOSAPENT_DFNDT00006897.

⁶⁷⁰ Takaku at ICOSAPENT_DFNDT00006897.

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

3 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
4 Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
5 studies cited by Defendants suggest that EPA increases LDL-C.⁶⁷¹ Defendants identify no other
6 basis upon which a person of ordinary skill would have sought to combine the Omacor
7 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

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

11 Defendants contend that the asserted claims of the '728 patent would have been obvious
12 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
13 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
14 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
15 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
16 very high TG patient population.

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

24 ⁶⁷¹ See, e.g., Rambjor.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
2 patient population were abnormally high and would not have relied upon these results. Further,
3 the person of skill in the art would not have looked to this patient population to predict the Apo-
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
6 levels.⁶⁷² Nozaki does not provide a motivation or reasonable expectation of success for
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
12 the EPA and the DHA content in the composition that was administered is unknown. A person
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
15 C were not statistically significant.⁶⁷³ Further, the person of skill in the art would not have
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
21 administered to the very high TG patient population.

23 ⁶⁷² Nozaki at 256.

24 ⁶⁷³ Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not
2 placebo controlled. This study would not have been extrapolated to Western populations
3 because the Japanese diet contains much more fish and has a number of other different attributes.
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western
5 populations. In fact, Defendants' own reference states that the results from studies where the
6 patient population is exclusively Japanese cannot be generalized to other populations.⁶⁷⁴ The
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
10 the Japanese respond differently to lipid lowering agents than Westerners.

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

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

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
21 C levels."⁶⁷⁵ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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23 ⁶⁷⁴ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

24 ⁶⁷⁵ Defendants' Joint Invalidity Contentions at 209.

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

14 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
15 that “DHA was responsible for the increase in LDL-C levels.”⁶⁷⁶ The discussion related to
16 Grimsgaard in Section V.A.3.c.1.a.ii.a.i and Mori 2000 in Section V.A.3.c.1.a.i.a.iii is
17 incorporated herein by reference.

18 Defendants argue that Maki discloses the administration of purified DHA resulted in the
19 desired reduction of TGs, but also significantly increased LDL-C levels.⁶⁷⁷ Maki was designed
20 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
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23 ⁶⁷⁶ Defendants’ Joint Invalidation Contentions at 206.

24 ⁶⁷⁷ Defendants’ Joint Invalidation Contentions at 209.

1 below-average levels of HDL-C levels.⁶⁷⁸ The DHA supplemented group was administered
2 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
3 monounsaturated and polyunsaturated fatty acids.⁶⁷⁹ Therefore, Maki demonstrated that when
4 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
5 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
6 observed.⁶⁸⁰ However, one cannot attribute the rise in LDL-C solely to DHA, because the
7 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
8 also contributed to the elevation in LDL cholesterol.”⁶⁸¹ Further, Maki admits that the
9 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
10 supplementation are not fully understood.”⁶⁸² Therefore, the results of Maki are inconclusive as
11 to DHA’s effect alone on LDL-C levels.

12 Defendants mischaracterize the rise in LDL-C associated with the administration of
13 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
14 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
15 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
16 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
17 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
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19

20 ⁶⁷⁸ Maki at 190.

21 ⁶⁷⁹ Maki at 191.

22 ⁶⁸⁰ Maki at 195.

23 ⁶⁸¹ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

24 ⁶⁸² Maki at 197.

1 less worrisome.”⁶⁸³ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
2 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
3 “less worrisome” because of the “potentially favorable effects on triglycerides, the
4 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
5 particles.”⁶⁸⁴

6 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
7 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
9 has little effect on LDL-C levels.⁶⁸⁵ Defendants identify no other basis upon which a person of
10 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
11 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

12 (iii) The ‘728 Patent Is Not Obvious Over the
13 Omacor PDR/Lovaza PDR, in Combination
14 with Katayama in View of Satoh and/or in
View of Satoh or Shinozaki in Further View
of Contacos

15 With respect to the ‘728 Patent, Defendants present a combination of five references: “the
16 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
17 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
18 further view of Contacos.”⁶⁸⁶ Defendants also present charts purporting to assert that an
19 additional 60 references may be combined in order to render the Claims obvious. Not only do
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21 ⁶⁸³ Maki at 197.

22 ⁶⁸⁴ Maki at 197.

23 ⁶⁸⁵ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ⁶⁸⁶ Defendants’ Joint Invalidity Contentions at 206-07.

1 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
2 references, they additionally do not suggest any identify for combining these references.
3 Although Defendants need not point to an explicit statement in the prior art motivating the
4 combination of these references, any assertion of an “apparent reason” to combine must find a
5 basis in the factual record.⁶⁸⁷ Defendants’ unsupported cobbling of selective disclosures
6 represents hindsight reconstruction.⁶⁸⁸ Defendants’ contentions are no more than an assertion
7 that certain claim elements were known in the prior art. Throughout their contentions,
8 Defendants’ selectively cite to data points in a reference without considering other disclosures or
9 even the reference as a whole. Each reference, however, must be evaluated for all that it
10 teaches.⁶⁸⁹ Accordingly, Defendants fail to meet their burden to establish *prima facie*
11 obviousness.

12 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
13 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
14 acid compositions or administration period. The Lovaza PDR further does not disclose a method
15

16 ⁶⁸⁷ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁶⁸⁸ 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”).

⁶⁸⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

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

8 Defendants formulate an obviousness argument that relies on Contacos.⁶⁹⁰ However,
9 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
10 element, an “apparent reason” or motivation to combine the elements in the manner claimed,⁶⁹¹
11 or “a reasonable expectation of success”⁶⁹² of achieving the claimed invention.

12 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
13 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
14 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
15 population and does not provide any reasonable expectation of success in lowering TG levels in
16 the very high TG patient population without increasing LDL-C. Contacos also fails to provide
17 motivation to administer purified EPA to a very high TG patient population and does not provide
18

19 ⁶⁹⁰ *Id.*

20 ⁶⁹¹ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ⁶⁹² *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

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

3 The proposed combinations do not render the independent claims of the '728 Patent
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
5 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
6 and the Lovaza package insert specifically) during prosecution.⁶⁹³

7 With respect to Claims 8 and 19, Defendants contend, without support, that “[a]s there is
8 no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been
9 obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without
10 increasing LDL-C, in this manner, with a reasonable expectation of success.” Defendants further
11 contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the
12 recited amount because there is no significance attached to the amount. Defendants conclude,
13 without support, that there was a reasonable expectation of success without identifying any
14 combination of references and without explaining how each reference relates to the claimed
15 invention.⁶⁹⁴ These contentions are inadequate to establish *prima facie* obviousness.

16 Because Defendants do not identify any combination of references, they necessarily fail
17 to offer any evidence that a person of skill in the art would be motivated to combine those
18 references in order to achieve the invention of the claim as a whole. Defendants make a
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20 ⁶⁹³ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
21 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”).

22 ⁶⁹⁴ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
23 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
24 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
2 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
3 person of ordinary skill to reduce triglycerides by the recited amount.⁶⁹⁵ Defendants’ burden to
4 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
5 attached to the recited TG reduction amount.⁶⁹⁶ Defendants have not met the burden with the
6 naked assertion that it would have been obvious to seek the claim element.

7 Similarly, without the disclosure of a combination of references and a motivation/reason
8 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
9 person of ordinary skill in the art would have had a reasonable expectation of success in
10 achieving the claimed invention. Defendants make a conclusory statement that there was a
11 reasonable expectation of success, without providing a support other than merely identifying
12 prior art references that purportedly disclose disparate elements.⁶⁹⁷ The mere fact that elements
13 are capable of being physically combined does not establish reasonable expectation of success.⁶⁹⁸

14
15 ⁶⁹⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
16 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
17 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
18 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)).

19 ⁶⁹⁶ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
20 established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

21 ⁶⁹⁷ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
22 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
quotation marks omitted).

23 ⁶⁹⁸ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

1 Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting
2 TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively.
3 Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per
4 day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.⁶⁹⁹
5 Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient*
6 *population*, and does not provide any reasonable expectation of success in lowering TG levels in
7 the very high TG patient population without increasing LDL-C. Defendants discuss the claim
8 elements in isolation, and fail to address the claimed invention as a whole.⁷⁰⁰ Defendants
9 selectively cite to an unspecified isolated disclosure within a reference without considering other
10 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
11 that it teaches.⁷⁰¹ Defendants’ unsupported cobbling of selective disclosures represents hindsight
12 reconstruction.⁷⁰²

13 The analysis of the independent claims of the ’728 Patent is incorporated into all asserted
14 claims that depend from those Claims.

15 (a) A Person of Ordinary Skill Would
16 Not Have Been Motivated to
17 Replace the Mixed Fish Oil Active

20 ⁶⁹⁹ See Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

21 ⁷⁰⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
22 made with respect to the subject matter as a whole, not separate pieces of the claim”).

23 ⁷⁰¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁷⁰² 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”).

For an invention to be obvious, there must have been an “apparent reason” to make it. The subject matter of the ‘728 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.A.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.⁷⁰³ Defendants’

⁷⁰³ Satoh at 145.

1 characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be
2 a “clinical benefit” is incorrect.⁷⁰⁴ Satoh does not disclose or suggest that the LDL-C results
3 obtained were a clinical benefit, nor would a person of ordinary skill view these references as
4 teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in
5 the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh
6 provides no evidence to the contrary. A person of ordinary skill in the art, however, would have
7 expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in
8 patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA
9 to a very high TG patient population and does not provide any reasonable expectation of success
10 in lowering TG levels in the very high TG patient population without increasing LDL-C.

11 Further, Satoh was a small study conducted in only Japanese patients. This study would
12 not have been extrapolated to Western populations because the Japanese diet contains much
13 more fish and has a number of other different attributes. The Japanese consume a higher amount
14 of EPA and DHA in their diets than Western populations. In fact, Defendants’ own reference
15 states that the results from studies where the patient population is exclusively Japanese cannot be
16 generalized to other populations.⁷⁰⁵ The Japanese diet comprises between 8 and 15 times more
17 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
18 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
19 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
20 agents than Westerners.

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23 ⁷⁰⁴ Defendants’ Joint Invalidity Contentions at 205-06.

24 ⁷⁰⁵ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
2 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
3 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
4 increasing LDL-C to be a "clinical benefit" is incorrect.⁷⁰⁶ Shinozaki says nothing about an
5 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
6 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."⁷⁰⁷ In
7 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
8 upon which a person of ordinary skill would have sought to combine the composition disclosed
9 in Shinozaki.

10 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
11 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
12 Defendants suggest that EPA increases LDL-C.⁷⁰⁸ Defendants identify no other basis upon
13 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
14 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

18 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
19 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
20 C levels."⁷⁰⁹ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

22 ⁷⁰⁶ Defendants' Joint Invalidation Contentions at 205-06.

23 ⁷⁰⁷ Shinozaki at 107-109.

24 ⁷⁰⁸ See, e.g., Rambjor.

⁷⁰⁹ Defendants' Joint Invalidation Contentions at 209.

1 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
2 rely on to support this statement do not categorize the increase in LDL-C as a “negative effect”
3 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
4 patients in Geppert and Kelley had normal and borderline-high/high baseline TG levels,
5 respectively. As discussed above in Section III, a person of ordinary skill would not expect the
6 same LDL-C effect in patients with lower baseline TG levels—the subjects of Geppert and/or
7 Kelley—as in very-high TG patients because patients with higher TG levels had different lipid
8 responses compared to patients with lower TG levels. Patients with very-high TG levels were
9 considered fundamentally different from patients with borderline-high or high triglycerides from
10 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Although a
11 person of ordinary skill in the art would have expected that fish oils (and other TG lowering
12 agents) would not increase LDL-C substantially in patients with normal to borderline high TG
13 levels, a person of ordinary skill in the art would expect a substantial increase in LDL-C in
14 patients with very high TG levels.

15 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
16 was responsible for the increase in LDL-C levels.”⁷¹⁰ Both Geppert and Kelley administer
17 DHA-rich oil that contained other saturated and polyunsaturated fatty acids. Therefore, a person
18 of ordinary skill would have known it is unsuitable for evaluating the independent effects of
19 DHA because it is not clear how much of the supplement’s effects can be attributed to DHA.⁷¹¹

22 _____
23 ⁷¹⁰ Defendants’ Joint Invalidity Contentions at 207.

24 ⁷¹¹ See Mori 2006 at 96.

1 For example, Defendants’ own prior art teaches that changes in fatty acid intake other than DHA,
2 particularly palmitate, may contribute to elevations in LDL-C.⁷¹²

3 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
4 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
5 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
6 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”⁷¹³ Rather than reading
7 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
8 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
9 was confusion in the art and it was unclear whether DHA increased LDL-C.

10 A person of ordinary skill would have expected that Geppert’s results would be
11 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
12 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
13 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
14 explain the mechanism of LDL-C increase.⁷¹⁴ A person of ordinary skill would have not
15 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

16 Defendants contend that Kelley shows that DHA was responsible for the increase in
17 LDL-C.⁷¹⁵ In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
18 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
19 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
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21 ⁷¹² Maki at 197.

22 ⁷¹³ Geppert at 784.

23 ⁷¹⁴ *Id.*

24 ⁷¹⁵ Defendants’ Joint Invalidity Contentions at 207.

1 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
2 therapy.⁷¹⁶ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
3 context with the other lipid effects reported in the study. Kelley states that:

4 DHA supplementation may lower the risk of CVD by reducing
5 plasma triacylglycerols; triacylglycerol:HDL; the number of
6 small, dense LDL particles; and mean diameter of VLDL particles.
7 An increase was observed in fasting LDL cholesterol, but it
8 is unlikely this increase is detrimental because no increase was
9 observed in the overall number of LDL particles; actually, there
10 was an 11% reduction that was statistically not significant. The
11 reason LDL cholesterol increased despite no change in LDL
12 particle number was that the LDL particles were made larger and
13 hence more cholesterol rich by DHA treatment.⁷¹⁷

14 Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation
15 is unlikely to be “detrimental” because there was not a parallel increase in overall LDL particle
16 number. Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
17 concentrations of atherogenic lipids and lipoproteins and increased concentrations of
18 cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular
19 health.”⁷¹⁸ Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
20 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
21 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
22 negative attributes, a person of ordinary skill would understand that the reference taught towards
23 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
24 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,

22 ⁷¹⁶ Kelley at 329.

23 ⁷¹⁷ Kelley at 329

24 ⁷¹⁸ Kelley at 324, 332.

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

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

7 Throughout their contentions, Defendants' selectively cite to data points in a reference
8 without considering other disclosures or even the reference as a whole. Each reference,
9 however, must be evaluated for all that it teaches.⁷¹⁹ As is the case with Kelley, Defendants use
10 hindsight to characterize a reference based on LDL-C levels alone without considering the other
11 lipid effects studied, considered and reported.⁷²⁰ The isolated manner in which Defendants select
12 such data points is not the approach that a person of ordinary skill would have taken at the time
13 of the invention. Defendants' approach represents the use of impermissible hindsight bias. A
14 person of ordinary skill would take into consideration the entire disclosure of a reference,
15 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
16 without explanation, the other effects of DHA that a person of ordinary skill would consider.
17 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
18 favorable effect in hypertriglyceridemic patients.

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

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22 ⁷¹⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁷²⁰ Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.").

1 without explanation, other studies that demonstrate that DHA decreases or has little effect on
2 LDL-C levels.⁷²¹ Defendants identify no other basis upon which a person of ordinary skill would
3 have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert
4 and/or Kelley.

5 (iv) A Person of Ordinary Skill Would Not Have
6 Been Motivated to Find an Omega-3 Fatty
7 Acid “therapy that would reduce TG levels
8 in patients with TG levels ≥ 500 mg/dL
9 without negatively impacting LDL-C
10 levels.”

11 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
12 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
13 was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,
14 or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels
15 for very-high TG patients at the time of the invention. A person of ordinary skill in the art
16 understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and
17 Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were
18 available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription
19 omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly
20 undesirable side effects—including “flushing” (or reddening of the face and other areas with a
21 burning sensation) and dyspepsia—that limited their usefulness.⁷²² Fibrates were effective at
22 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG
23 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an
24

22 ⁷²¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

23 ⁷²² See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher
24 doses of niacin due to side effects).

1 LDL-C lowering medication such as a statin.⁷²³ However, the risk of rhabdomyolysis increased
 2 five-fold if fibrates were administered with a statin.⁷²⁴ Therefore, physicians were reluctant to
 3 recommend, and patients were hesitant embrace, a combination fibrate/statin course of
 4 treatment.⁷²⁵ Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to
 5 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,
 6 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

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

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁷²⁶	-20%	+45%
Lovaza/Omacor ⁷²⁷	-6%	+45%

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 16 That Epadel has been approved for decades but not approved for use in the very high TG
 17 patient population prior to the invention of the asserted patents is a real-world reflection of the
 18 lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s.
 19 In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have

20 ⁷²³ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is
 21 often required to achieve LDL-C and non-HDL-C goals”);

22 ⁷²⁴ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with
 23 statins.”).

24 ⁷²⁵ See *Id.*, ¶ 17

⁷²⁶ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

⁷²⁷ Chan 2002 I at 2381 (Table 3).

1 | been countless studies conducted which administer EPA and report the effects observed.
2 | Although a few studies administer EPA to a patient population which included a few patients
3 | with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the
4 | administration of EPA to patients with very-high TG levels, reflecting the lack of motivation.

5 | Defendants offer no “apparent reason” to administer EPA as claimed to patients with
6 | fasting baseline TG levels of 500 mg/dl to about 1500 mg/dl. Defendants rely on
7 | Lovaza/Omacor as the starting point to “find a therapy that would reduce TG levels in patients
8 | with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels.”⁷²⁸ Ironically,
9 | Lovaza/Omacor significantly reduces TGs in patients with TG levels of at least 500 mg/dL but
10 | significantly increases LDL-C--an effect understood to be a consequence of TG reduction and
11 | the increased conversion of VLDL to LDL particles.⁷²⁹

12 | It was well known at the time of the invention that omega-3 fatty acids, including both
13 | EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
14 | increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
15 | fatty acids worked in part by inhibiting VLDL production and improving the conversion of
16 | VLDL particles to LDL.⁷³⁰ A person of ordinary skill in the art understood that EPA and DHA
17 | had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
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19 |

20 | ⁷²⁸ Defendants’ Joint Invalidity Contentions at 208.

21 | ⁷²⁹ See Bays 2008 Rx Omega-3 p. 402; McKenny 2007 Role of Prescription Omega-3 at 720 (finding that “[t]hese
22 | results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and
secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

23 | ⁷³⁰ Chan 202 at 2378-84; see also Westphal at 917 (stating “our data confirm the well-known and pronounced
24 | decrease in VLDLs after n-3 fatty acid treatment”)

1 discussing the TG-lowering mechanism of omega-3 fatty acids.⁷³¹ The discussion related to the
2 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
3 incorporated herein by reference.

4 In fact, it was well understood that the degree of LDL-C elevation observed with
5 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
6 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
7 the most in patients with the highest pretreatment TG levels.⁷³² Therefore, a person of ordinary
8 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
9 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-
10 C was often offset by concurrent treatment with statins.⁷³³ The safety and efficacy of using
11 prescription omega-3 in combination with a statin has been well-established.⁷³⁴

12 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
13 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
14 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.
15 Therefore, the final LDL-C concentration may still be in the normal range.⁷³⁵ Furthermore, it
16 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.⁷³⁶

17
18 ⁷³¹ 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))

19 ⁷³² See Bays 2008 Rx Omega-3 p. 402.

20 ⁷³³ See Harris 2008 at 14, McKenney at 722.

21 ⁷³⁴ McKenney at 722-23.

22 ⁷³⁵ See Westphal at 918, Harris 1997 at 389.

23 ⁷³⁶ See Pownall at 295 (stating that “[t]reatment with ω -3 fatty acids appear to change the lipid profile of individuals
24 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester transfer activity), serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he 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

1 In two pivotal studies in very-high TG patients, both of which used prospective,
2 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
3 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).⁷³⁷ Correspondingly, prescription
4 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.⁷³⁸ Therefore,
5 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
6 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
7 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
8 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
9 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
10 number of small, dense LDL particles to larger LDL particles.⁷³⁹ Lovaza/Omacor “adversely
11 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
12 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”⁷⁴⁰ Therefore,
13 one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids
14 generally, “for the treatment of severe hypertriglyceridemia may be beneficial not only for the
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16
17

18 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
19 pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
20 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
21 acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
22 LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
23 decreased non-HDL-C levels (TC minus HDL-C)”).

21 ⁷³⁷ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

22 ⁷³⁸ McKenney 2007 at 722 (see Fig. 1).

23 ⁷³⁹ McKenney 2007 at 722 (citing Calabresi and Stalenhoef).

24 ⁷⁴⁰ Stalenhoef at 134.

1 short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary
2 heart disease].”⁷⁴¹

3 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
4 the time of the claimed inventions would have been motivated to find a therapy that would
5 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
6 LDL-C levels,”⁷⁴² one of ordinary skill in the art at the time of the invention understood that the
7 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
8 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
9 increase in very-high TG patients, and in some instances the rise was not concerning because
10 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
11 concentration would still be in the normal range. When LDL-C levels increased beyond what
12 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively
13 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
14 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
15 identify any other basis upon which a person of ordinary skill would have been motivated to find
16 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
17 impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood
18 that EPA therapy would *not* reduce Apo-B⁷⁴³ (which is a reflection of total atherogenic
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22 ⁷⁴¹ Harris 1997 at 389.

23 ⁷⁴² Defendants’ Joint Invalidity Contentions at 208.

24 ⁷⁴³ *see* Section V.O.

1 lipoproteins)⁷⁴⁴ in very high TG patients, and accordingly would not have been motivated to
2 administer the claimed EPA composition to the very high TG patient population.

3 Defendants make the conclusory allegation that “routine optimization” by a person of
4 ordinary skill would yield the claimed invention.⁷⁴⁵ Defendants, however, have offered no
5 explanation to support that allegation and they further fail to establish any of the required criteria
6 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
7 factual detail to support their allegation and they fail to link the allegation to any particular claim
8 or claim element. Defendants mere allegation constitute an improper placeholder to later
9 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
10 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
11 combinations alleged by Defendants and, for the same reasons, it would not be routine to
12 combine such references. Where, for example, defendants argue that it would be routine to go
13 from the high TG patient population to the very high TG patient population,⁷⁴⁶ they provide no
14 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
15 would have understood these patient populations to be distinct with different impacts of lipid
16 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
17 not have considered the dosage modification suggested by defendants to be routine; Defendants’
18 argument to the contrary represents hindsight bias.

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22 _____
⁷⁴⁴ see Section III.

23 ⁷⁴⁵ See, e.g., Defendants’ Joint Invalidation Contentions at 197, 204-205.

24 ⁷⁴⁶ Defendants’ Joint Invalidation Contentions at 236.

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

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

8 Defendants provide no evidence that a person of ordinary skill would have had a
9 reasonable expectation of successfully obtaining the claimed invention—a method of reducing
10 triglycerides in a subject having very-high triglyceride levels by administering EPA of the
11 recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by
12 combining the references cited by defendants. For a particular combination of references, there
13 must be a reasonable expectation that the combination will produce the claimed invention. In
14 this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with
15 very-high TG levels.⁷⁴⁷ A person of ordinary skill would have expected EPA, like
16 Lovaza/Omacor, to raise LDL-C levels when administered to patients in the very-high TG
17 patient population. As discussed in Section III and above, it was well known that TG-lowering
18 agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for
19 normal to high TG patients, but caused significant increases in LDL-C levels for patients with
20 very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary
21 skill to expect anything to the contrary. A person of ordinary skill would have understood that

22 ⁷⁴⁷ As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to
23 have the same TG lowering mechanism and would have further understood that the increase in LDL-C
24 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar
fashion to Lovaza or DHA alone.

1 omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among
2 very high TG patients, as reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁷⁴⁸	-20%	+45%
Lovaza/Omacor ⁷⁴⁹	-6%	+45%

6 Accordingly, a person of ordinary skill would *not* have a reasonable expectation of
7 success in achieving a reduction in TG levels without substantially increasing LDL-C in patients
8 with very-high TG levels.⁷⁵⁰

9
10 Defendants' position that a person of ordinary skill would have had a reasonable
11 expectation of success in administering purified EPA to patients with very high triglyceride
12 levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that
13 Defendants' provide no evidence that anyone thought to administer Epadel.⁷⁵¹ Epadel was
14 available for many years prior to the invention of the '728 patent, to patients with very-high TGs
15 as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,
16 to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of
17 EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by
18 Defendants are directed to the use of purified EPA in the very-high TG population.

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21 ⁷⁴⁸ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

22 ⁷⁴⁹ Chan 2002 I at 2381 (Table 3).

23 ⁷⁵⁰ Indeed, as discussed above, a person of ordinary skill would have understood that DHA had a better overall effect
on lipid parameters, teaching away from this combination.

24 ⁷⁵¹ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not
examined in any study directed to the very-high TG patient population supports Amarin's position.

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

10 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
11 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
12 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
13 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
14 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.⁷⁵²
15 Defendants' contentions are no more than a demonstration that certain claim elements was
16 known in the prior art and demonstrates impermissible hindsight reconstruction.⁷⁵³ As is
17 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,
18 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA
19 and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that
20 administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,

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22 ⁷⁵² Defendants' Joint Invalidity Contentions at 210-11.

23 ⁷⁵³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under KSR,
24 "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.").

1 none of these references would provide a person of ordinary skill in the art with a reasonable
 2 expectation of successfully obtaining the claimed invention even if there were reasons to
 3 combine disparate, independent elements found in the prior art, which there were not.

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

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triclycerols (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 ³	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 ³	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
LDL: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 ³	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 $\bar{x} \pm SD$.
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.

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

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

21 To the extent that Defendants' arguments are based on results that are not statistically
 22 significant and not reported by Grimsgaard as significant, a person of ordinary skill would not
 23

1 draw conclusions from these statistically insignificant differences. Indeed, the standard
2 deviation for the changes reported is greater than the value of the change itself.

3 Defendants argue that it would have been obvious to try administering purified ethyl EPA
4 to patients with very-high TG levels with a reasonable expectation of success. However, the
5 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-
6 try” proves that the claimed invention was obvious where the prior art did not suggest what to
7 try.⁷⁵⁴ Rather than there being a limited number of options, the state of the art provided a
8 plethora of compositions and administration protocols associated with multiple kinds of TG-
9 lowering therapies.⁷⁵⁵ There were not a finite number of options for a person of ordinary skill
10 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
11 population.

12 Defendants argue that a person of ordinary skill at the time of the invention, based on
13 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone
14 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to
15 no impact on LDL-C levels.⁷⁵⁶ However, that statement does not conform with what was known
16 regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG
17 patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor were
18 both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

19 With the lack of any reasonable expectation of success, Defendants argue that their
20 proposed combination amounts to a simple substitution of one known element for another, and
21

22 ⁷⁵⁴ See *Sanofi*, 748 F.3d at 1360–61.

23 ⁷⁵⁵ See *supra* Section III.

24 ⁷⁵⁶ Defendants’ Joint Invalidity Contentions at 210.

1 that that these changes yield predictable results.⁷⁵⁷ Such an argument, however, represents pure
2 and impermissible hindsight bias and further does not consider that reasons for which a person of
3 ordinary skill would not be motivated to combine these references and affirmatives ways in
4 which the art taught away from these combinations.

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

7 (i) The '728 Patent is not Obvious Over WO
8 '118 or WO '900, in Combination with the
Lovaza PDR, and Further in View of Leigh-
9 Firbank and/or Mori 2000

10 With respect to the '728 Patent, Defendants present a combination of five references:
11 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the
12 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."⁷⁵⁸ Defendants also
13 present charts arguing that an additional 61 references may be combined in order to render the
14 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill
15 would combine 61 separate references, they additionally do not identify any motivation for
16 combining these references.^{759, 760} Although Defendants need not point to an explicit statement

17 ⁷⁵⁷ Defendants' Joint Invalidity Contentions at 211.

18 ⁷⁵⁸ Defendants' Joint Invalidity Contentions at 213.

19 ⁷⁵⁹ Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in
20 V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama,
Matsuzawa, Matakai, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki,
21 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
22 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 213.

23 ⁷⁶⁰ Defendants' bare assertion that "the motivation or reason to combine or modify the prior art to create invalidating
24 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

1 in the prior art motivating the combination of these references, any assertion of an “apparent
2 reason” to combine must find a basis in the factual record.⁷⁶¹ Defendants’ unsupported cobbling
3 of selective disclosures represents hindsight reconstruction.⁷⁶² Defendants’ contentions are no
4 more than an assertion that certain claim elements were known in the prior art. Throughout their
5 contentions, Defendants’ selectively cite to data points in a reference without considering other
6 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
7 that it teaches.⁷⁶³ Accordingly, Defendants fail to meet their burden to establish *prima facie*
8 obviousness.

9 WO ‘118 is directed at the composition containing EPA for the purpose of preventing the
10 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO ‘118
11 is directed, “in particular, [to] preventing occurrence of cardiovascular events in
12 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the

13
14
15 ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or
modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidation Contentions at 203-04.

16 ⁷⁶¹ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
18 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (stating that the assertion of a starting point
19 “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.
20 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
21 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).

22 ⁷⁶² *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
23 any explanation as to how or why the references would be combined to produce the claimed invention”).

24 ⁷⁶³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 risk of the cardiovascular events.”⁷⁶⁴ Contrary to Defendants’ assertion that WO ‘118 discloses
2 “the administration of 4 g of pure EPA with no DHA,”⁷⁶⁵ WO ‘118 fails to disclose the claimed
3 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive
4 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified
5 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction
6 without substantially increasing LDL-C. WO ‘118 discloses a composition with a wide range of
7 possible EPA content, dosages, and teaches that DHA is a “preferable fatty acid” to include in
8 the disclosed composition.⁷⁶⁶

9 WO ‘118 does not disclose administration of highly-purified ethyl-EPA to the target
10 population of the claimed invention. The asserted claims are directed to persons with severe
11 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO ‘118 on the other hand only
12 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.⁷⁶⁷ WO
13 ‘118’s emphasis on reducing cardiovascular events suggests that its disclosure is directed to
14 patients with borderline-high to high TG levels, since the primary goal for patients with very-
15 high TG is to prevent acute pancreatitis by decreasing TG levels.⁷⁶⁸

16 WO ‘118 also does not distinguish EPA from DHA in its disclosures regarding the
17 effectiveness of the substances for treating hypertriglyceridemia.⁷⁶⁹ WO ‘118 states that
18

19 _____
⁷⁶⁴ WO ‘118 at 9.

20 ⁷⁶⁵ Defendants’ Joint Invalidity Contentions at 213.

21 ⁷⁶⁶ WO ‘118 at 22-23.

22 ⁷⁶⁷ WO ‘118 at 8.

23 ⁷⁶⁸ See Section III.

24 ⁷⁶⁹ WO ‘118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective component”).

1 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-
2 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
3 DHA-E) are not particularly limited as long as intended effects of the present invention are
4 attained.”⁷⁷⁰ It further states that “the composition is preferably the one having a high purity of
5 EPA-E and DHA-E.”⁷⁷¹ Further, WO ’118 does not disclose EPA’s effect on LDL-C, VLDL-C,
6 Apo-B, or Lp-PLA2.

7 WO ’900 is directed to a process for producing purified EPA from a culture of micro-
8 organisms. WO ’900 fails to disclose the claimed subject with the specified very high TG levels
9 (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed
10 pharmaceutical composition with the specified dosage or administration period, or the claimed
11 method to effect the specified TG reduction without substantially increasing LDL-C. WO ’900
12 only discloses the method of producing purified EPA for therapeutic use, it does not teach
13 *administration* of pure EPA. WO ’900 has no discussion, for example, regarding claimed patient
14 population or method of treatment.

15 WO ’900 does not teach administration of pure EPA to treat hypertriglyceridemia. It
16 lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one
17 of them.⁷⁷² Moreover, WO ’900 does not teach the desired effect of EPA other than commenting
18 generally that it “may promote health and ameliorate or even reverse the effects of a range of
19 common diseases.”⁷⁷³ It has no discussion, for example, on any TG-lowering effect of EPA.

21 ⁷⁷⁰ WO ’118 at 22-23.

22 ⁷⁷¹ WO ’118 at 23.

23 ⁷⁷² See, e.g., ’900 Pub. at 16-17.

24 ⁷⁷³ ’900 Pub. at 5.

1 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
2 undesired effect of DHA or other impurities it is trying to prevent other than commenting
3 generally that “the desired effects of EPA may be limited or reversed” by them.⁷⁷⁴ It has no
4 discussion related to any LDL-C effects caused by DHA.

5 The proposed combination does not render the independent claims of the '728 Patent
6 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
7 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
8 insert specifically) during prosecution.⁷⁷⁵

9 With respect to Claims 8 and 19, Defendants contend, without support, that “[a]s there is
10 no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been
11 obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without
12 increasing LDL-C, in this manner, with a reasonable expectation of success.” Defendants further
13 contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the
14 recited amount because there is no significance attached to the amount. Defendants conclude,
15 without support, that there was a reasonable expectation of success without identifying any
16 combination of references and without explaining how each reference relates to the claimed
17 invention.⁷⁷⁶ These contentions are inadequate to establish *prima facie* obviousness.

19 ⁷⁷⁴ '900 Pub. at 39.

20 ⁷⁷⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
21 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”).

22 ⁷⁷⁶ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
23 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
24 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Because Defendants do not identify any combination of references, they necessarily fail
2 to offer any evidence that a person of skill in the art would be motivated to combine those
3 references in order to achieve the invention of the claim as a whole. Defendants make a
4 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
5 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
6 person of ordinary skill to reduce triglycerides by the recited amount.⁷⁷⁷ Defendants’ burden to
7 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
8 attached to the recited TG reduction amount.⁷⁷⁸ Defendants have not met the burden with the
9 naked assertion that it would have been obvious to seek the claim element.

10 Similarly, without the disclosure of a combination of references and a motivation/reason
11 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
12 person of ordinary skill in the art would have had a reasonable expectation of success in
13 achieving the claimed invention. Defendants make a conclusory statement that there was a
14 reasonable expectation of success, without providing a support other than merely identifying
15
16
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18 ⁷⁷⁷ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
19 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
20 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
21 quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir.
22 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)).

23 ⁷⁷⁸ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
24 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).

1 prior art references that purportedly disclose disparate elements.⁷⁷⁹ The mere fact that elements
2 are capable of being physically combined does not establish reasonable expectation of success.⁷⁸⁰

3 Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting
4 TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively.

5 Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per
6 day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.⁷⁸¹

7 Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient*
8 *population*, and does not provide any reasonable expectation of success in lowering TG levels in

9 the very high TG patient population without increasing LDL-C. Defendants discuss the claim

10 elements in isolation, and fail to address the claimed invention as a whole.⁷⁸² Defendants

11 selectively cite to an unspecified isolated disclosure within a reference without considering other

12 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

13 that it teaches.⁷⁸³ Defendants' unsupported cobbling of selective disclosures represents hindsight

14 reconstruction.⁷⁸⁴

16 ⁷⁷⁹ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
17 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
18 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
19 quotation marks omitted).

20 ⁷⁸⁰ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
21 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
22 combined, but also that the combination would have worked for its intended purpose.”).

23 ⁷⁸¹ See Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

24 ⁷⁸² *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”).

⁷⁸³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

⁷⁸⁴ See, e.g., *Immogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
“[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

1 The analysis of the independent claims of the ‘728 patent is incorporated into all asserted
2 claims that depend from those Claims.

3 (a) Leigh-Firbank and Mori 2000 Do
4 Not Disclose Purported Knowledge
5 that DHA was Responsible for the
6 Increase in LDL-C

7 Defendants contend that a “person of ordinary skill in the art would have been motivated
8 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
9 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
10 C levels as evidenced by Leigh-Firbank or Mori 2000.”⁷⁸⁵

11 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with
12 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
13 not point to an explicit statement in the prior art motivating the combination of these references,
14 any assertion of an “apparent reason” to combine must find a basis in the factual record.⁷⁸⁶
15 Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁷⁸⁷
16 Defendants’ contentions are no more than an assertion that certain claim elements were known in

17 ⁷⁸⁵ Defendants’ Joint Invalidity Contentions at 214.

18 ⁷⁸⁶ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
19 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
20 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
21 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
22 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
23 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
24 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁷⁸⁷ See, e.g., *Imogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR,
“[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

1 the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie*
2 obviousness.

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

16 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it
17 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
18 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
19 effect on LDL-C levels.⁷⁸⁸ Defendants identify no other basis upon which a person of ordinary
20 skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or
21 Mori.

22 (ii) The '728 Patent is not Obvious Over WO
23 '118, WO '900, Grimsgaard, Mori 2000

24 ⁷⁸⁸ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 and/or Maki in Combination with the
2 Omacor PDR/Lovaza PDR, and Further in
3 View of Katayama, Matsuzawa and/or
4 Takaku.

5 With respect to the '728 Patent, Defendants present a combination of nine references:

6 “WO '118, WO '900 , Grimsgaard, Mori 2000 and/or Maki in combination with treatment
7 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view
8 of Katayama, Matsuzawa and/or Takaku.”⁷⁸⁹ Defendants also present charts arguing that an
9 additional 56 references may be combined in order to render the Claims obvious. Not only do
10 Defendants ignore the improbability that a person of ordinary skill would combine 56 separate
11 references, they additionally do not identify any motivation for combining these references.
12 Although Defendants need not point to an explicit statement in the prior art motivating the
13 combination of these references, any assertion of an “apparent reason” to combine must find a
14 basis in the factual record.⁷⁹⁰ Defendants’ unsupported cobbling of selective disclosures
15 represents hindsight reconstruction.⁷⁹¹ Defendants’ contentions are no more than an assertion

16 ⁷⁸⁹ Defendants’ Joint Invalidity Contentions at 214.

17 ⁷⁹⁰ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

⁷⁹¹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR,
“[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that certain claim elements were known in the prior art. Throughout their contentions,
2 Defendants’ selectively cite to data points in a reference without considering other disclosures or
3 even the reference as a whole. Each reference, however, must be evaluated for all that it
4 teaches.⁷⁹² Accordingly, Defendants fail to meet their burden to establish *prima facie*
5 obviousness.

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

15 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
16 to use EPA as described in WO ‘118, WO ‘900 , Grimsgaard or Mori 2000 in the treatment
17 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
18 assertions fail to provide a motivation for combining the references.⁷⁹³ Although Defendants
19 need not point to an explicit statement in the prior art motivating the combination of these
20 references, any assertion of an “apparent reason” to combine must find a basis in the factual
21

22 _____
23 ⁷⁹² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁷⁹³ Defendants’ Joint Invalidity Contentions at 214.

1 record.⁷⁹⁴ Defendants’ assertions related to motivation are insufficient,⁷⁹⁵ and accordingly
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
6 manner claimed,⁷⁹⁶ or “a reasonable expectation of success”⁷⁹⁷ of achieving the claimed
7 invention. Therefore, Defendants should be precluded from relying on this these references.

8 As discussed above in Section V.A.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
10

11
12 ⁷⁹⁴ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
13 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
14 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
15 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
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17 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
18 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
19 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
20 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
21 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
22 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
23 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

17 ⁷⁹⁵ For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
18 hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
19 basis for that statement. While the paragraph associated with that statement makes assertions regarding the
20 disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
21 ’118. See Defendants’ Joint Invalidity Contentions at 214.

20 ⁷⁹⁶ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
23 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ⁷⁹⁷ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
2 purified EPA to the very high TG patient population and do not provide any reasonable
3 expectation of success in lowering TG levels in the very high TG patient population without
4 increasing LDL-C. As discussed above in Section V.A.3.c.1.a.ii.a.i, Takaku candidly
5 acknowledges that “only a few subjects were examined” and cautions against drawing a
6 conclusion “only from the results of the present study.”⁷⁹⁸ Further, the study did not include any
7 placebo control, therefore, a person of ordinary skill in the art would understand these reports do
8 not provide the ability to conclude that the observed lipid effects would have occurred
9 independent of the drug that is administered. In addition, the study was conducted exclusively in
10 Japanese patients, and a person of ordinary skill would not have expected the results to be
11 applicable to the general population.⁷⁹⁹

12 The proposed combination does not render the independent claims of the '728 Patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.⁸⁰⁰

16 With respect to Claims 8 and 19, Defendants contend, without support, that “[a]s there is
17 no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been
18 obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without
19 increasing LDL-C, in this manner, with a reasonable expectation of success.” Defendants further

20 _____
21 ⁷⁹⁸ Takaku at ICOSAPENT_DFNDT00006897.

22 ⁷⁹⁹ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

23 ⁸⁰⁰ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the
2 recited amount because there is no significance attached to the amount. Defendants conclude,
3 without support, that there was a reasonable expectation of success without identifying any
4 combination of references and without explaining how each reference relates to the claimed
5 invention.⁸⁰¹ These contentions are inadequate to establish *prima facie* obviousness.

6 Because Defendants do not identify any combination of references, they necessarily fail
7 to offer any evidence that a person of skill in the art would be motivated to combine those
8 references in order to achieve the invention of the claim as a whole. Defendants make a
9 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
10 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
11 person of ordinary skill to reduce triglycerides by the recited amount.⁸⁰² Defendants’ burden to
12 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
13 attached to the recited TG reduction amount.⁸⁰³ Defendants have not met the burden with the
14 naked assertion that it would have been obvious to seek the claim element.

16 ⁸⁰¹ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
17 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
18 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

19 ⁸⁰² *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
20 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
21 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
22 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)).

23 ⁸⁰³ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
24 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).

1 Similarly, without the disclosure of a combination of references and a motivation/reason
2 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
3 person of ordinary skill in the art would have had a reasonable expectation of success in
4 achieving the claimed invention. Defendants make a conclusory statement that there was a
5 reasonable expectation of success, without providing a support other than merely identifying
6 prior art references that purportedly disclose disparate elements.⁸⁰⁴ The mere fact that elements
7 are capable of being physically combined does not establish reasonable expectation of success.⁸⁰⁵

8 Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting
9 TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively.
10 Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per
11 day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.⁸⁰⁶
12 Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient*
13 *population*, and does not provide any reasonable expectation of success in lowering TG levels in
14 the very high TG patient population without increasing LDL-C. Defendants discuss the claim
15 elements in isolation, and fail to address the claimed invention as a whole.⁸⁰⁷ Defendants
16 selectively cite to an unspecified isolated disclosure within a reference without considering other
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19 ⁸⁰⁴ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
20 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).

21 ⁸⁰⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
22 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

23 ⁸⁰⁶ See Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

24 ⁸⁰⁷ *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”).

1 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
2 that it teaches.⁸⁰⁸ Defendants’ unsupported cobbling of selective disclosures represents hindsight
3 reconstruction.⁸⁰⁹

4 The analysis of the independent claims of the ‘728 patent is incorporated into all asserted
5 claims that depend from those Claims.

6 (a) Grimsgaard, Mori 2000 and/or Maki
7 Do Not Disclose Purported
8 Knowledge that DHA was
9 Responsible for the Increase in LDL-
10 C

11 Defendants contend that a “person of ordinary skill in the art would have been motivated
12 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
13 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
14 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
15 Maki.”⁸¹⁰

16 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
17 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
18 Mori 2000 and/or Maki in Section V.A.3.c.1.a.ii.a.iii is incorporated herein by reference. A
19 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
20 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
21 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
22 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not

23 ⁸⁰⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ⁸⁰⁹ *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”).

⁸¹⁰ Defendants’ Joint Invalidity Contentions at 214.

1 disclose administration of DHA to the requisite patient population and teaches that DHA is
2 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
3 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
4 would consider. Most controlled studies in patients with normal to high baseline TG levels
5 indicated that DHA had little or no effect on LDL-C.⁸¹¹ Therefore, a person of ordinary skill
6 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
7 TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is
8 administered to patients with below-average levels of HDL-C levels and borderline-high TG
9 levels, a significant increase in LDL-C is observed.⁸¹² However, one of ordinary skill in the art
10 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.⁸¹³
11 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

12 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
13 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
14 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
15 has little effect on LDL-C levels.⁸¹⁴ Defendants identify no other basis upon which a person of
16 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,
17 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

19 ⁸¹¹ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
20 controlled, found an increase in LDL-C after DHA administration.

21 ⁸¹² Maki at 195.

22 ⁸¹³ 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
23 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.”).

24 ⁸¹⁴ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

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

5 For an invention to be obvious, there must have been an “apparent reason” to make it.
6 Defendants assert that a “person of ordinary skill in the art would have been motivated to
7 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
8 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”⁸¹⁵ However, as
9 set forth below, Defendants fail to address why a person of ordinary skill in the art would have
10 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
11 greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering
12 triglycerides *without increasing LDL-C levels*.

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

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁸¹⁶	-20%	+45%
Lovaza/Omacor ⁸¹⁷	-6%	+45%

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22 _____
23 ⁸¹⁵ Defendants’ Joint Invalidity Contentions at 215.

24 ⁸¹⁶ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

⁸¹⁷ Chan 2002 I at 2381 (Table 3).

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

9 Defendants further argue that the disclosure in WO '118 would combine with the prior art
10 concerning Lovaza for at least two reasons; first, "products containing DHA were reported to
11 increase LDL-C levels while products containing only EPA did not," and second, "WO '118
12 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
13 purified ethyl-EPA."⁸¹⁸ Both of the "reasons" identified by Defendants are false.

14 Regarding Defendants' first reason, that "products containing DHA were reported to
15 increase LDL-C levels while products containing only EPA did not," most controlled studies in
16 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
17 LDL-C.⁸¹⁹ Therefore, a person of ordinary skill would not have concluded that DHA increases
18 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
19 and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease,
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22 ⁸¹⁸ Defendants' Joint Invalidation Contentions at 215.

23 ⁸¹⁹ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
24 controlled, found an increase in LDL-C after DHA administration.

1 while EPA does not.”⁸²⁰ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
2 alone because it did not administer EPA and DHA separately.⁸²¹ A person of ordinary skill
3 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
4 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
5 on lipid parameters. Second, Kelley administered DHA-rich oil that contained other saturated
6 and polyunsaturated fatty acids.⁸²² Therefore, a person of ordinary skill would have known it is
7 unsuitable for evaluating the independent effects of DHA because it is not clear how much of the
8 supplement’s effects can be attributed to DHA.⁸²³ Kelley does not show that DHA is responsible
9 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
10 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
11 therapy.⁸²⁴ Kelley specifically teaches that the increase in LDL-C caused by DHA
12 supplementation is unlikely to be “detrimental” because there was not a parallel increase in
13 overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a
14 rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA
15 had uniquely beneficial cardioprotective effects.⁸²⁵ Finally, Theobald also does not teach that
16 DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in
17 patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when
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19 ⁸²⁰ Defendants’ Joint Invalidation Contentions at 220.

20 ⁸²¹ The discussion related to Leigh-Firbank in Section V.A.3.c.1.a.i.a.iii is incorporated herein by reference.

21 ⁸²² The discussion related to Kelley in Section V.A.3.c.1.a.iii.a.ii is incorporated herein by reference.

22 ⁸²³ See Mori 2006 at 96.

23 ⁸²⁴ Kelley at 329.

24 ⁸²⁵ Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins” and that “DHA supplementation may improve cardiovascular health.”)

1 compared to placebo. However, the DHA composition that was administered in Theobald
2 contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic
3 acid.⁸²⁶ Therefore, a person of ordinary skill would have known that the DHA administered by
4 Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to
5 determine whether or how much of the supplement’s effects can be attributed to DHA.⁸²⁷
6 Contrary to Defendants’ assertion that there was “a reported advantage to using EPA vs. DHA in
7 hypertriglyceridemic subjects,”⁸²⁸ there was no known advantage to using EPA vs. DHA. In
8 fact, a number of the references Defendants cite in their contentions ultimately conclude that
9 DHA supplementation “may represent a more favorable lipid profile than after EPA
10 supplementation.”⁸²⁹ In addition, a person of ordinary skill would have recognized any impact of
11 DHA reported by the study to be applicable to EPA because they would have understood these
12 substances to function by the same mechanism. Furthermore, as discussed above in Section III, a
13 person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline
14 TG levels, including healthy patients, as in very-high TG patients because patients with higher
15 TG levels had different lipid responses compared to patients with lower TG levels.

16 Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in
17 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”
18 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
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21 ⁸²⁶ Theobald at 560.

22 ⁸²⁷ See Mori 2006 at 96.

23 ⁸²⁸ Defendants’ Joint Invalidation Contentions at 215.

24 ⁸²⁹ Mori 2000 at 1092.

1 well documented.⁸³⁰ Lovaza/Omacor has been shown to reduce the risk for cardiovascular death
2 plus nonfatal myocardial infarction and nonfatal stroke.⁸³¹ Omega-3 fatty acids have been shown
3 to exert cardioprotective effects in both primary and secondary coronary heart disease prevention
4 trials.⁸³² Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic
5 effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart
6 rate.⁸³³

7 Defendants argue that a “person of ordinary skill in the art would have appreciated the
8 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
9 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
10 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”⁸³⁴ As
11 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
12 and Lovaza/Omacor have been well documented.⁸³⁵

13 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
14 disease endpoints as a function of tissue FA composition found that the evidence suggested that
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17 ⁸³⁰ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
18 *ATHEROSCLEROSIS*, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA
19 and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

20 ⁸³¹ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 *AM. J. CARDIOL* 71i (2006) (“Bays 2006”).

21 ⁸³² Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 *ATHEROSCLEROSIS* 12, 13 (2008) (“Harris 2008”).

22 ⁸³³ Harris 2008 at 13.

23 ⁸³⁴ Defendants’ Joint Invalidation Contentions at 216.

24 ⁸³⁵ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.”) (“Harris 2007”).

1 DHA is *more* cardioprotective than EPA.⁸³⁶ This study found that “depressed levels of long-
2 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
3 heart disease events.”⁸³⁷ Further, the study found that DHA levels, with or without EPA, were
4 significantly lower in fatal endpoints.⁸³⁸ This study suggests that DHA is preferable to EPA—
5 thus teaching away from the claimed invention.⁸³⁹ Defendants rely on hindsight bias to argue
6 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
7 and DHA were known to have cardioprotective effects, and there were studies suggesting DHA
8 was *more* cardioprotective than EPA.

9 Defendants argue that the following claim elements were known: the administration of
10 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
11 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
12 patients with high and very high TG levels who were not receiving concurrent lipid altering
13 therapy, and the dose of 4g/day and 12-week regimen.⁸⁴⁰ Defendants then argue that the “only
14 question is whether one skilled in the art would have been motivated to use the DHA-free,
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18 ⁸³⁶ Harris 2007 at 8.

19 ⁸³⁷ *Id.*

20 ⁸³⁸ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all studies,
21 suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

22 ⁸³⁹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
23 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
24 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.”).

⁸⁴⁰ Defendants’ Joint Invalidity Contentions at 217.

1 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
2 least 500 mg/dL as part of the claimed dosage regimen.”⁸⁴¹

3 Defendants’ contentions are no more than a recitation that certain claim elements were
4 known in the prior art. Defendants’ assertions to the contrary represent hindsight
5 reconstruction.⁸⁴² Notably, Defendants *do not* assert that a person of ordinary skill would have
6 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
7 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,⁸⁴³
8 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
9 number of prior art references disclosed the administration of purified EPA to patients with TG
10 levels > 500 mg/dL.”^{844, 845} The disclosures of Nakamura (one patient), Matsuzawa (disclosure
11 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the
12 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of
13 ordinary skill in the art would *not* understand these references to relate to the use of EPA in
14 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions
15 regarding these references in terms of the very high TG patient population. In Nakamura, one
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18 ⁸⁴¹ Defendants’ Joint Invalidity Contentions at 217.

19 ⁸⁴² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under KSR,
20 “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention.”).

21 ⁸⁴³ Nakamura, Matsuzawa, and Takaku.

22 ⁸⁴⁴ Defendants’ Joint Invalidity Contentions at 217.

23 ⁸⁴⁵ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
24 mg/dL. Hayashi states that the baseline TG level was 300 ± 233 mg/dL. However, the standard error is unusually
high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically
states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

1 patient had a baseline TG level > 500 mg/dL.⁸⁴⁶ However, the mean baseline TG for all patients
2 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was
3 well below 500 mg/dL.⁸⁴⁷ In Matsuzawa, three patients had TG levels between 400 and 1000
4 mg/dL and one patient had TG levels > 1,000 mg/dL.⁸⁴⁸ Based on this disclosure, only one
5 patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one patient was excluded
6 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol
7 made it impossible to assess triglyceride levels.”⁸⁴⁹ In Takaku, three patients had baseline TG
8 levels above 500 mg/dL.⁸⁵⁰ However, the mean baseline TG level for all patients was 245
9 mg/dL.⁸⁵¹ Indeed, the mean baseline TG level of the patients in all three studies was well below
10 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be
11 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,
12 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the
13 Friedewald’s Equation cannot be used for patients with triglyceride levels \geq 400 mg/dL.⁸⁵²
14 Defendants have failed to identify all of the claimed elements and fail to provide motivation to
15 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with
16 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

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⁸⁴⁶ Nakamura at 23, Table 1.

20 ⁸⁴⁷ Nakamura at 23, Tables 1 and 2.

21 ⁸⁴⁸ *Id.* at 23.

22 ⁸⁴⁹ *Id.* at 10.

23 ⁸⁵⁰ Takaku at ICOSAPENT_DFNDTS00006895.

24 ⁸⁵¹ Takaku at ICOSAPENT_DFNDTS00006875.

⁸⁵² *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

1 Defendants contend that a “person of ordinary skill in the art would have been motivated
2 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
3 known TG-lowering effects of highly-purified EPA-E.”⁸⁵³ This argument is flawed. The prior
4 art demonstrates a wide range of administration periods utilized in different clinical studies. For
5 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
6 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
7 Given the large number of choices of administration periods disclosed in prior art, Defendants
8 have not shown that a person of ordinary skill would not have been motivated to administer
9 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

10 Moreover, a person of ordinary skill would not have been motivated to administer highly-
11 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
12 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
13 triglycerides.⁸⁵⁴ In fact, Defendants acknowledge in their Joint Invalidity Contentions that
14 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
15 another.”⁸⁵⁵ Data from some studies even suggested that DHA or fish oil may reduce
16 triglyceride more effectively than EPA.⁸⁵⁶ Therefore, a person of ordinary skill would not have
17 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
18 of EPA and DHA (such as Lovaza) for 12 weeks.

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⁸⁵³ Defendants’ Joint Invalidity Contentions at 218.

21 ⁸⁵⁴ Mori 2006 at 98.

22 ⁸⁵⁵ Defendants’ Joint Invalidity Contentions at 222.

23 ⁸⁵⁶ Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
24 (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
grater with DHA supplementation than EPA supplementation).

1 Defendants argue that a “person of ordinary skill in the art also would have been
2 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
3 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.⁸⁵⁷ This
4 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
5 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
6 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

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

10 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
11 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
12 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
13 dose of 4 g/day rather than a lower dose.”⁸⁵⁸ A person of ordinary skill would not have relied on
14 either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
15 because these studies were not designed to determine the effect of dose on the degree of TG
16 reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower
17 dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

18 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
19 triglycerides.⁸⁵⁹ Therefore, a person of ordinary skill would not have been motivated to
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⁸⁵⁷ Defendants’ Joint Invalidation Contentions at 218.

23 ⁸⁵⁸ Defendants’ Joint Invalidation Contentions at 218.

24 ⁸⁵⁹ See Section III.

1 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
2 EPA and DHA (such as Lovaza).

3 Defendants further argue that a “person of ordinary skill in the art would have also been
4 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
5 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
6 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
7 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”⁸⁶⁰ This argument is
8 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
9 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
10 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
11 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
12 TG levels above 500 mg/dL. Further, a person of ordinary skill would have expected that a
13 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
14 increase in LDL-C levels.

15 Defendants contend that a “person of ordinary skill in the art would have been motivated
16 to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a
17 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
18 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”⁸⁶¹ Defendants first
19 support this argument by asserting that a person of ordinary skill in the art would have known
20 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
21 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
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23 ⁸⁶⁰ Defendants’ Joint Invalidity Contentions at 218.

24 ⁸⁶¹ Defendants’ Joint Invalidity Contentions at 219.

1 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
2 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
3 V.B.4. and 5” to support this proposition,⁸⁶² however these references do not disclose or suggest
4 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
5 high TG patients.⁸⁶³

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

11 Defendants argue that a person of ordinary skill in the art “would have known that an
12 increase in LDL-C was an adverse health effect to be avoided.”⁸⁶⁴ While an increase in LDL-C
13 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
14 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
15 fatty acids generally, was related to increased conversion of VLDL to LDL particles.⁸⁶⁵

16 Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the
17 art would have been motivated, with a reasonable expectation of success, to administer a highly-
18 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in
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20 ⁸⁶² Defendants’ Joint Invalidation Contentions at 219-20.

21 ⁸⁶³ *See* Section IV.

22 ⁸⁶⁴ Defendants’ Joint Invalidation Contentions at 221.

23 ⁸⁶⁵ *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
24 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
levels when given prescription omega-3 therapy”); Chan 2003.

1 LDL-C with DHA.”⁸⁶⁶ However, a person of ordinary skill in the art expected an increase in
2 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
3 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
4 decrease in the production of VLDL particles and a significant increase in the conversion of
5 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
6 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.⁸⁶⁷ A
7 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
8 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
9 mechanism of omega-3 fatty acids.⁸⁶⁸ The discussion related to the TG-lowering mechanism of
10 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

11 Further, a person of ordinary skill in the art would have understood that EPA therapy
12 would *not* reduce Apo-B⁸⁶⁹ (which is a reflection of total atherogenic lipoproteins)⁸⁷⁰ in very
13 high TG patients, and accordingly would not have been motivated to administer the claimed EPA
14 composition to the very high TG patient population.

15 Accordingly, a person of ordinary skill would not have been motivated to combine WO
16 ‘118, WO ‘900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
17 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
18 have been motivated to combine WO ‘118 or WO ‘900, with the Lovaza PDR, or with Leigh-
19 Firbank and/or Mori 2000.

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21 ⁸⁶⁶ Defendants’ Joint Invalidity Contentions at 222.

22 ⁸⁶⁷ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
decrease in VLDLs after n-3 fatty acid treatment”).

23 ⁸⁶⁸ Bays 2008 I, at 398; Bays *in* Kwiterovich at 247.

24 ⁸⁶⁹ *see* Section V.O.

⁸⁷⁰ *see* Section III.

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

5 Defendants contend that a “person of ordinary skill in the art would have been motivated
6 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal
7 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”⁸⁷¹ Defendants
8 also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would
9 have given a person of ordinary skill in the art a reasonable expectation of successfully
10 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
11 these subjects relative to baseline or placebo.”⁸⁷² However, Defendants provide no evidence that
12 a person of ordinary skill would have had a reasonable expectation of success in a method of
13 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
14 EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore,
15 Defendants fail to provide a reasonable expectation of success for the claimed invention.

16 Defendants further argue, that “because it was known that DHA and EPA were
17 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
18 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
19 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been
20 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition
21 with a reasonable expectation of success that such administration would result in reducing
22 triglycerides while avoiding an increase in LDL.”⁸⁷³ Defendants argument is without any basis.

23 ⁸⁷¹ Defendants’ Joint Invalidity Contentions at 215.

24 ⁸⁷² Defendants’ Joint Invalidity Contentions at 219.

⁸⁷³ Defendants’ Joint Invalidity Contentions at 223.

1 To the contrary, because a person of ordinary skill in the art would have understood DHA and
 2 EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have
 3 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
 4 explanation and cite to no article to support their argument that the similar effects on TG levels is
 5 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
 6 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
 7 both EPA and DHA, whether administered alone or in combination, would cause an increase in
 8 LDL-C when administered to the very high TG patient population.

9 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
 10 with very-high TG. A person of ordinary skill would have thus expected EPA, like
 11 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
 12 population. It was well known that TG-lowering agents, specifically fibrates and
 13 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
 14 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
 15 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
 16 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
 17 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
 18 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ⁸⁷⁴	-20%	+45%
Lovaza/Omacor ⁸⁷⁵	-6%	+45%

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

875 Chan 2002 I at 2381 (Table 3).

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

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to the requisite patient population to achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel, which was available for many years prior to the invention of the '728 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.

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(2) Dependent Claims

(a) Defendants Have Not Shown that Claims 2, 3, 9 and 10 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1 and 8 and 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 2, 3, 9 and 10.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claims 2, 3, 9 and 10. Defendants contend, without providing any support, that the claim elements are the results of simply optimizing the conditions described in the prior art and within the purview of the skilled physicians. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. None of the cited references discloses administration of the claimed EPA to very high TG patients. Defendants further fail to explain how the cited references can be

1 combined to teach the administration of the claimed EPA to very high TG patients.⁸⁷⁶
2 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
3 considering other disclosures or even the reference as a whole. Each reference, however, must
4 be evaluated for all that it teaches.⁸⁷⁷ Defendants’ unsupported cobbling of selective disclosures
5 represents hindsight reconstruction.⁸⁷⁸

6 Defendants fail to show a motivation or reason to combine or modify the references
7 recited above. Defendants make a conclusory statement that the claimed methods of treatment
8 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not
9 show why a person of ordinary skill would have been motivated to combine the references to
10 achieve the claimed invention.⁸⁷⁹

11 Defendants fail to show a reasonable expectation that a person of ordinary skill would
12 have successfully achieved the claimed invention. In fact, other than simply identifying prior art
13 references that purportedly disclose disparate elements, Defendants do not even discuss whether
14 a person of ordinary skill would have expected that the combination to work for its intended
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18 ⁸⁷⁶ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 ⁸⁷⁷ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ⁸⁷⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ⁸⁷⁹ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
23 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).
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1 purpose.⁸⁸⁰ As such, Defendants fail to demonstrate reasonable expectation of success of the
2 claimed invention.

3 (b) Defendants Have Not Shown that Claims 4 and 11
4 of the '728 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and
6 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by
7 clear and convincing evidence, they also have not adequately proven the obviousness of Claims
8 4 and 11.

9 Defendants do not identify any combination of references and simply provide a laundry
10 list of references without explaining how each reference relates to the claimed invention.
11 Defendants further contend, without any support, that a person of ordinary skill would have been
12 able to determine the patient population in need of the claimed methods of treatment, would seek
13 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat
14 those patients having very high triglycerides regardless of the baseline values of these lipids.⁸⁸¹
15 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
16 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
17 combination of claim elements were all present in the prior art references that would have been
18 combined by a person of ordinary skill in the art to produce the claimed invention with a
19 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
20 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
21 element out of the claim. Although convenient and expedient, Defendants' approach does not

22 ⁸⁸⁰ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
24 combined, but also that the combination would have worked for its intended purpose.”)

⁸⁸¹ *Id.*

1 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
2 obviousness.

3 Defendants fail to show a specific combination of references that discloses each element
4 of the claimed invention. Defendants merely list references, without reference to a specific page
5 or section, that purportedly disclose disparate elements without explaining how they can be
6 combined.⁸⁸² As such, Defendants discuss the claim elements in isolation, and fail to address the
7 claimed invention as a whole.⁸⁸³ Moreover, by simply identifying prior art references without
8 discussing the specific teachings of each reference, Defendants fail to consider each prior art
9 reference as a whole.⁸⁸⁴ Each reference must be evaluated for all that it teaches. Defendants’
10 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁸⁸⁵

11 Because Defendants do not identify any combination of references, they necessarily fail
12 to offer any evidence that a person of skill in the art would be motivated to combine those
13 references in order to achieve the invention of the claim as a whole. Defendants make a
14 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed
15 methods of treatment, without providing a reason that would have prompted a person of ordinary
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18 ⁸⁸² *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
19 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

20 ⁸⁸³ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

21 ⁸⁸⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior
22 patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention
in suit.”) (internal citation and quotation marks omitted).

23 ⁸⁸⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
24 “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

1 skill to combine the elements.⁸⁸⁶ Such a naked assertion does not show why a person of ordinary
2 skill would have been motivated to treat the recited patient population using the claimed methods
3 of treatment.⁸⁸⁷

4 Similarly, without the disclosure of a combination of references and a motivation/reason
5 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
6 person of ordinary skill in the art would have had a reasonable expectation of success in
7 achieving the claimed invention. In fact, other than simply identifying prior art references that
8 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
9 ordinary skill would have expected that the combination to work for its intended purpose for
10 treating the recited patient population.⁸⁸⁸ As such, Defendants fail to demonstrate reasonable
11 expectation of success of the claimed invention.

12 (c) Defendants Have Not Shown that Claims 5 and 12
13 of the '728 Patent Would Have Been Obvious

14 Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and
15 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by
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18 ⁸⁸⁶ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
19 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)

20 ⁸⁸⁷ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
22 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁸⁸⁸ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 clear and convincing evidence, they also have not adequately proven the obviousness of Claims
2 5 and 12.

3 Defendants contend that EPA is known to reduce non-HDL-C and VLDL-C levels.
4 Defendants further contend that a person of ordinary skill would have a reasonable expectation
5 that a composition comprising EPA, but not DHA, would lower non-HDL-C levels, citing a
6 laundry list of references without explaining how each reference relates to the claimed
7 invention.⁸⁸⁹ These contentions: 1) do not assert what the prior art discloses to a person of
8 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
9 specific combination of claim elements were all present in the prior art references that would
10 have been combined by a person of ordinary skill in the art to produce the claimed invention
11 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.
12 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
13 reading the element out of the claim. Although convenient and expedient, Defendants' approach
14 does not conform with the Local Patent Rules of this District, the law of claim construction, or
15 the law of obviousness.

16 Defendants do not identify any combination of references and simply provide a laundry
17 list of references that purportedly disclose disparate elements without explaining how they can
18 be combined.⁸⁹⁰ As such, Defendants discuss the claim elements in isolation, and fail to address
19 the claimed invention as a whole.⁸⁹¹ Defendants selectively cite to an unspecified isolated

20 ⁸⁸⁹ *Id.*

21 ⁸⁹⁰ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

23 ⁸⁹¹ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 disclosure within a reference without considering other disclosures or even the reference as a
2 whole. Each reference, however, must be evaluated for all that it teaches.⁸⁹² Defendants’
3 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁸⁹³

4 Because Defendants do not identify any combination of references, they necessarily fail
5 to offer any evidence that a person of skill in the art would be motivated to combine those
6 references in order to achieve the invention of the claim as a whole. In fact, Defendants do not
7 discuss at all whether a person of ordinary skill would have been motivated to combine the
8 elements.⁸⁹⁴ As such, Defendants fail to demonstrate that there was no motivation to combine
9 the references to achieve the claimed invention.

10 Similarly, without the disclosure of a combination of references and a motivation/reason
11 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
12 person of ordinary skill in the art would have had a reasonable expectation of success in
13 achieving the claimed invention. Defendants make a conclusory statement that a person of
14 ordinary skill “would have a reasonable expectation that a composition comprising EPA, but not
15 DHA would lower non-HDL-C levels,” without providing a support other than simply
16 identifying prior art references that purportedly disclose disparate elements.⁸⁹⁵ The mere fact
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18 ⁸⁹² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ⁸⁹³ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
20 “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ⁸⁹⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁸⁹⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
24 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning

1 that elements are capable of being physically combined does not establish reasonable expectation
2 of success.⁸⁹⁶ What is more, Defendants do not even discuss the reasonable expectation of
3 reducing non-HDL-C and VLDL-C levels. As such, Defendants fail to demonstrate reasonable
4 expectation of success of reducing non-HDL-C and VLDL-C levels using the claimed methods.

5 (d) Defendants Have Not Shown that Claims 6 and 13
6 of the '728 Patent Would Have Been Obvious

7 Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and
8 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by
9 clear and convincing evidence, they also have not adequately proven the obviousness of Claims
10 6 and 13.

11 Defendants contend, without support, that the recited reduction in TG represents
12 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
13 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
14 ordinary skill to seek to reduce TG by the recited amount because there is no significance
15 attached to the amount. Defendants conclude, without support, that there was a reasonable
16 expectation of success without identifying any combination of references and without explaining
17 how each reference relates to the claimed invention.⁸⁹⁷ These contentions: 1) do not assert what
18 the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious

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20 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
quotation marks omitted).

21 ⁸⁹⁶ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
22 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

23 ⁸⁹⁷ *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
24 *2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,*
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

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

8 Defendants do not identify any combination of references and simply provide a laundry
9 list of references that purportedly disclose disparate elements without explaining how they can
10 be combined.⁸⁹⁸ As such, Defendants discuss the claim elements in isolation, and fail to address
11 the claimed invention as a whole.⁸⁹⁹ Defendants selectively cite to an unspecified isolated
12 disclosure within a reference without considering other disclosures or even the reference as a
13 whole. Each reference, however, must be evaluated for all that it teaches.⁹⁰⁰ Defendants'
14 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁹⁰¹

15 Because Defendants do not identify any combination of references, they necessarily fail
16 to offer any evidence that a person of skill in the art would be motivated to combine those
17 references in order to achieve the invention of the claim as a whole. Defendants make a
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19 ⁸⁹⁸ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

21 ⁸⁹⁹ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ⁹⁰⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁹⁰¹ See, e.g., *Immogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
24 “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

1 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
2 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
3 person of ordinary skill to reduce triglycerides by the recited amount.⁹⁰² Defendants’ burden to
4 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
5 attached to the recited TG reduction amount.⁹⁰³ Defendants have not met the burden with the
6 naked assertion that it would have been obvious to seek the claim element.

7 Similarly, without the disclosure of a combination of references and a motivation/reason
8 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
9 person of ordinary skill in the art would have had a reasonable expectation of success in
10 achieving the claimed invention. Defendants make a conclusory statement that there was a
11 reasonable expectation of success, without providing a support other than merely identifying
12 prior art references that purportedly disclose disparate elements.⁹⁰⁴ The mere fact that elements
13 are capable of being physically combined does not establish reasonable expectation of success.⁹⁰⁵
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15 ⁹⁰² *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
16 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
17 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
18 quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir.
19 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in
20 an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a
21 person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in
22 an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁹⁰³ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
24 established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical”) (internal quotation marks omitted).

21 ⁹⁰⁴ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
22 by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning
23 to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal
24 quotation marks omitted).

23 ⁹⁰⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

1 (e) Defendants Have Not Shown that Claims 7 and 14
2 of the '728 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and
4 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by
5 clear and convincing evidence, they also have not adequately proven the obviousness of Claims
6 7 and 14. Claims 7 and 14 additionally include the claim element of administering to the subject
7 about 4g of the claimed pharmaceutical composition for a period of 12 weeks to effect a
8 reduction in fasting Lp-PLA2 of at least 10% compared to the second subject.

9 Defendants' contentions fail to disclose each and every element of the claims of the '560
10 patent. Specifically, Defendants do not contend that the relied upon references disclose the
11 following element of Claim 7: *administering the claimed pharmaceutical composition to the*
12 *recited subject to effect a reduction in fasting Lp-PLA2 of at least 10% compared to the second*
13 *subject.* Therefore, Defendants' prior art combinations cannot render the claims *prima facie*
14 obvious.

15 Defendants contend that "Virani discloses the correlation between Lp-PLA2 and Apo-B,"
16 and that Zalewski discloses that Lp-PL2 co-travels with LDL. Defendants then conclude,
17 without support, that "one of ordinary skill in the art would expect that the claimed methods
18 would reduce Apo-B, discussed above, and would therefore also reduce Lp-PLA2 with a
19 reasonable expectation of success." Defendants further contend that "given the correlation
20 between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to
21 reduce Lp-PLA2 to therapeutic levels. . . [and] [a]s there is no significance provided by the
22 patentee regarding the various percentage reductions of Lp-PLA2, it would have been obvious"
23 to a person of ordinary skill to seek to reduce Lp-PLA2 by 5% and 15%, with reasonable
24

1 expectation of success.⁹⁰⁶ These contentions: 1) fail to address whether the specific combination
2 of claim elements were all present in the prior art references that would have been combined by a
3 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation
4 of success; and 2) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
5 analysis, but trivialize the claim element to the point of reading the element out of the claim.
6 Although convenient and expedient, Defendants’ approach does not conform with the Local
7 Patent Rules of this District, the law of claim construction, or the law of obviousness.

8 Virani, Zalewski and Shinozaki do not render Claims 7 or 14 obvious. None of the
9 references disclose or suggest the administration of the claimed pharmaceutical compound to
10 effect a reduction in fasting Lp-PLA2 of at least 10%.

11 Virani and Zalewski are both general review articles that discuss Lp-PLA2’s biological
12 role in atherosclerosis. Virani reviews the potential mechanisms by which Lp-PLA2 may
13 “participate in the pathogenesis of atherosclerosis and its clinical manifestations, namely,
14 coronary artery disease and stroke.”⁹⁰⁷ Zalewski is a highly technical review of the biological
15 role of Lp-PLA2 in atherosclerosis. Neither article suggests or even discusses the administration
16 of any omega-3 fatty acid and any possible effects on Lp-PLA2 that may result. Defendants
17 have failed to identify even a single a prior art reference that discloses the administration of the
18 claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 10%.
19 Defendants fail to provide a basis for their assertion that “one of ordinary skill in the art would
20 expect that the claimed methods would reduce Apo-B, discussed above, and would therefore also
21 reduce Lp-PLA2 with a reasonable expectation of success.” As discussed in Section V.O, a

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23 ⁹⁰⁶ Plaintiffs note that Defendants fail to address the specific claim element, which requires a “reduction in fasting
Lp-PLA2 of at least 10% compared to the second subject.”

24 ⁹⁰⁷ Virani at 97.

1 person of ordinary skill in the art did *not* expect that the claimed method would reduce Apo-B.
2 Defendants have failed to prove that a decrease in Apo-B would lead a person of ordinary skill in
3 the art to expect that Lp-PLA2 would also decrease simply because “Lp-PLA2 circulates bound
4 to LDL via Apolipoprotein B.” Defendants have further failed to meet their burden as they do no
5 articulate an “apparent reason” to combine the elements in the manner claimed,⁹⁰⁸ or offer an
6 argument related to “a reasonable expectation of success.”⁹⁰⁹

7 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
8 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Shinozaki
9 does not discuss Lp-PLA2. In fact, Defendants rely on portions of Shinozaki that discuss effects
10 of EPA administration on TG, total cholesterol, and lipoprotein (a) levels. Accordingly,
11 Shinozaki does not disclose or suggest the administration of the claimed pharmaceutical
12 compound to effect a reduction in fasting Lp-PLA2 of at least 10%.

13 Defendants do not provide any basis for their assertion that “given the correlation
14 between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to
15 reduce Lp-PLA2 levels to therapeutic levels.” Such an assertion does not provide any evidence
16 of motivation or reasonable expectation of success in achieving the claimed invention, including
17 the reduction in fasting Lp-PLA2 of at least 10%. Further, while Virani discloses that statins and
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20 ⁹⁰⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ⁹⁰⁹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 fibrates decrease Lp-PLA2, there is no mention of the use of omega-3 fatty acids.⁹¹⁰ Virani and
2 Zalewski disclose that further research needs to be conducted regarding the relationship between
3 Lp-PLA2 and atherosclerosis.⁹¹¹

4 Defendants fail to provide any factual basis to support their allegation of obviousness and
5 reasonable expectation of success. Accordingly claims 7 and 14 of the '728 Patent are not
6 obvious in light of Virani, Zalewski and/or Shinozaki.

7 (f) Defendants Have Not Shown that Claims 15 and 17
8 of the '728 Patent Would Have Been Obvious

9 Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and
10 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by
11 clear and convincing evidence, they also have not adequately proven the obviousness of Claims
12 15 and 17.

13 Defendants contend that it would be obvious to use the claimed methods to treat patients
14 who consume a Western diet, because cardiovascular disease is a leading cause of death in the
15 United States and most European countries, and because it was common practice to advise
16 patients receiving triglyceride-lowering treatments to maintain their diet. These contentions: 1)
17 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant
18 to an obvious analysis; 3) fail to address whether the specific combination of claim elements
19 were all present in the prior art references that would have been combined by a person of
20 ordinary skill in the art to produce the claimed invention with a reasonable expectation of

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22 ⁹¹⁰ Virani at 101.

23 ⁹¹¹ Virani at 101 (“Understanding the role of Lp-PLA2 provides further insights into the process of atherosclerosis
24 and vascular inflammation.”); Zalewski at 928 (“To this end, future mechanistic studies need to address whether this
approach abrogates inflammation in atherosclerotic tissue and produces favorable changes in intermediate
cardiovascular end points.”).

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

5 Defendants do not identify any combination of references and simply provide a list of
6 references that purportedly disclose disparate elements without explaining how they can be
7 combined.⁹¹² Defendants offer no support or explanation for their assertion that “it is a well-
8 known, common practice to advise patients receiving triglyceride-lowering treatments to
9 maintain their diet.” As an initial matter, Defendants’ assertion—even if true—does not support
10 their obviousness claim and Defendants do not explain the connection between “maintain[ing]”
11 diet and the asserted claim. Defendants offer a laundry list of citations that do not appear to
12 support their unexplained assertion. Further, Defendants discuss the claim elements in isolation,
13 and fail to address the claimed invention as a whole.⁹¹³ Defendants selectively cite to an
14 unspecified isolated disclosure within a reference without considering other disclosures or even
15 the reference as a whole. Each reference, however, must be evaluated for all that it teaches.⁹¹⁴
16 Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.⁹¹⁵

19 ⁹¹² *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

21 ⁹¹³ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ⁹¹⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ⁹¹⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
24 “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Because Defendants do not identify any combination of references, they necessarily fail
2 to offer any evidence that a person of skill in the art would be motivated to combine those
3 references in order to achieve the invention of the claim as a whole. Defendants merely state that
4 the cardiovascular disease is a leading cause of death in the United States and most European
5 countries, and do not explain how that would have prompted a person of ordinary skill to use the
6 claimed method to treat patients who consume a Western diet.⁹¹⁶

7 Similarly, without the disclosure of a combination of references and a motivation/reason
8 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
9 person of ordinary skill in the art would have had a reasonable expectation of success in
10 achieving the claimed invention. In fact, other than simply identifying prior art references that
11 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
12 ordinary skill would have expected that the combination to work for its intended purpose.⁹¹⁷ As
13 such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

14 (g) Defendants Have Not Shown that Claims 16 and 18
15 of the '728 Patent Would Have Been Obvious

16 Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and
17 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by
18 clear and convincing evidence, it also has not adequately proven the obviousness of Claims 16
19 and 18.

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21 ⁹¹⁶ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ⁹¹⁷ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants contend that WO '900 discloses EPA purity of over 90%, including 96%, and
2 that it teaches the desirability of excluding other fatty acid substances from the composition,
3 including DHA. Defendants further contend that the claims are obvious because “patentees have
4 not provided any explanation of significance relating to the 0.6% by weight value.” These
5 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;
6 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of
7 claim elements were all present in the prior art references that would have been combined by a
8 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation
9 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
10 analysis, but trivialize the claim element to the point of reading the element out of the claim.
11 Although convenient and expedient, Defendants’ approach does not conform with the Local
12 Patent Rules of this District, the law of claim construction, or the law of obviousness.

13 Defendants do not identify any combination of references and simply provide a laundry
14 list of references that purportedly disclose disparate elements without explaining how they can
15 be combined.⁹¹⁸ Defendants fail to cite a single reference that discloses administration of the
16 claimed EPA with no more than 0.6% of any fatty acid, other than EPA, to treat patients. Nor do
17 Defendant explain how the cited reference can be combined with other references to achieve the
18 claimed invention.⁹¹⁹ As such, Defendants discuss the claim elements in isolation, and fail to
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21 ⁹¹⁸ *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”).

22 ⁹¹⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).
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1 address the claimed invention as a whole.⁹²⁰ Defendants selectively cite to an unspecified
2 isolated disclosure within a reference without considering other disclosures or even the reference
3 as a whole. Each reference, however, must be evaluated for all that it teaches.⁹²¹ Defendants’
4 unsupported cobbling of selective disclosures represents hindsight reconstruction.⁹²²

5 Because Defendants do not identify any combination of references, they necessarily fail
6 to offer any evidence that a person of skill in the art would be motivated to combine those
7 references in order to achieve the invention of the claim as a whole. Defendants merely state that
8 WO ‘900 teaches the desirability of excluding other fatty acid substances from the composition,
9 and do not explain how that would have prompted a person of ordinary skill to limit the fatty
10 acid content of fatty acids other than EPA to no more than 0.6% by weight of all fatty acids
11 combined.⁹²³ In fact, WO ‘900 does not teach the specific undesired of effect of the impurities,
12 or to what extent the impurity content should be limited. Moreover, Defendants’ burden to
13 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
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18 ⁹²⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
19 made with respect to the subject matter as a whole, not separate pieces of the claim”).

20 ⁹²¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

21 ⁹²² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*,
22 “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without
23 any explanation as to how or why the references would be combined to produce the claimed invention”).

24 ⁹²³ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 attached to the recited impurity limit.⁹²⁴ Defendants have not met the burden with the naked
2 assertion that the claims are obvious.⁹²⁵

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. In fact, Defendants do not even discuss whether a person of
7 ordinary skill would have expected that the combination to work for its intended purpose.⁹²⁶ As
8 such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

9 **4. The '728 Patent is Not Invalid Under § 112**

10 a) Defendants Have Not Provided Demonstrated that the Claims of
11 the '728 Patent Are Invalid for Indefiniteness

12 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
13 the subject matter which the applicant regards as his invention.”⁹²⁷ Patent claims are valid in
14 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
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16 ⁹²⁴ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
17 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).

18 ⁹²⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be sustained
19 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)

20 ⁹²⁶ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
21 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.”)

22 ⁹²⁷ Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
23 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
24 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.

1 art about the scope of the invention” in light of the specification and the prosecution history.⁹²⁸

2 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
3 and “the certainty which the law requires in patents is not greater than is reasonable.”⁹²⁹

4 Defendants allege that a number of terms containing the phrases “about” and
5 “substantially” are indefinite. Defendants do not provide any reason why these terms are
6 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,
7 these terms are routinely used in patent claims, and are not *per se* indefinite.⁹³⁰ In particular,
8 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
9 indefinite.⁹³¹ Here, a person of ordinary skill would understand with reasonable certainty what is
10 claimed when the claims are read in light of the specification and prosecution history.⁹³²

11 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
12 indefinite.

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14 ⁹²⁸ *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

15 ⁹²⁹ *Id.* at 2129.

16 ⁹³⁰ *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms of
17 degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 ⁹³¹ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (Fed. Cir.
22 2010) (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

⁹³² *See generally* the ’728 patent and its prosecution history.

1 Defendants further allege that the terms “4g per day of a pharmaceutical composition
2 comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” and
3 “wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more
4 than about 0.6% by weight of all fatty acids combined” are indefinite. They contend that,
5 because there is no indication of how much of the pharmaceutical composition is composed of
6 fatty acids, by extension it is indefinite how much of each fatty acid is present in the
7 composition. This is incorrect. A claim can use a ratio to define amounts of components in a
8 product, using terms such as “percent by weight.”⁹³³ In light of the specification and prosecution
9 history, a person of ordinary skill would understand with reasonable certainty the range of
10 relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical
11 composition in relation to all fatty acids present.⁹³⁴ Therefore, these terms are not indefinite and
12 do not render the claims indefinite.

13 Defendants further allege that the term “who does not receive concurrent lipid altering
14 therapy” is indefinite. Defendants provide no basis for this allegation. In light of the
15 specification and the prosecution history, however, a person of ordinary skill in the art would
16 understand with reasonable certainty the scope of a “concurrent lipid altering therapy.”⁹³⁵
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20 ⁹³³ *T.F.H. Publications, Inc. v. Daskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

23 ⁹³⁴ See generally the '728 patent and its prosecution history.

24 ⁹³⁵ See generally the '728 patent and its prosecution history.

1 Moreover, lipid altering therapies are discussed in the patent specification.⁹³⁶ Therefore, the
2 phrase “concurrent lipid altering therapy” does not render the claim indefinite.

3 Defendants further allege that the term “consume a Western diet” is indefinite because it
4 is “too vague.” But the specification and the prosecution history describe (and even define) a
5 “Western diet.”⁹³⁷ In light of the specification and the prosecution history, a person of ordinary
6 skill would know with reasonable certainty the scope of the term “Western diet,” and therefore
7 the term does not render the claims indefinite.

8 Defendants also allege that it is impossible to ascertain the metes and bounds of
9 “compared to . . . a second subject having a fasting baseline triglyceride level of 500 mg/dl to
10 about 1500 mg/dl . . .” A person of ordinary skill, however, would understand the metes and
11 bounds of the term in light of the specification and the prosecution history.⁹³⁸ Moreover, the
12 method of comparing a subject to a second subject, such as a placebo controlled, randomized,
13 double blind study, would have been known to a person of ordinary skill at the time of the
14 invention. Therefore, the term does not render the claims indefinite.

15 Finally, Defendants contend that the asserted claims improperly mix methods and
16 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that
17 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
18 analysis is based on what the claim language informs a person of ordinary skill in the art in light
19 of the specification and the prosecution history. Defendants do not identify any actual claim
20 language that mixes methods and formulations. Moreover, contributory infringement may be

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22 ⁹³⁶ See e.g., ‘728 patent at 12:43-46; 13:66-5.

23 ⁹³⁷ See generally the ‘728 patent and its prosecution history; see e.g., ‘728 patent at 9:24-38.

24 ⁹³⁸ See generally the ‘728 patent and its prosecution history.

1 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*
2 *process* . . . knowing the same to be especially made or especially adapted for use in an
3 infringement of such patent.”⁹³⁹ Plaintiffs assert that Defendants’ ANDA products will be used
4 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
5 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are
6 mistaken and the ’728 patent claims are not indefinite for improperly mixing methods and
7 formulations.

8 b) Defendants Have Not Demonstrated that the Claims of the ’728
9 Patent Are Invalid for Insufficient Written Description

10 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a
11 written description of the invention.” This requires that the specification “reasonably convey” to
12 a skilled artisan that the applicant “invented” or “had possession” of the claimed subject matter
13 when the application was filed.⁹⁴⁰ Support need not be literal⁹⁴¹—it may be implicit⁹⁴² or
14 inherent⁹⁴³ in the disclosure. In addition, it is unnecessary to include information that is already
15 known or available to persons of ordinary skill.⁹⁴⁴

16 Defendants make three arguments regarding the written description requirement. First,
17 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack

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⁹³⁹ 35 U.S.C. § 271(c) (emphasis added).

19 ⁹⁴⁰ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

20 ⁹⁴¹ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

21 ⁹⁴² *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

22 ⁹⁴³ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

23 ⁹⁴⁴ *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.

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1 written description. This is incorrect. The specification of asserted patents literally discloses the
2 claimed invention.⁹⁴⁵ Moreover, the recited baseline TG levels of the claimed invention appear
3 in the original claims of the application to which the asserted patent claims priority. Thus, there
4 is a strong presumption that the claimed invention is adequately described.⁹⁴⁶ Defendants do not
5 and cannot rebut this presumption. Specifically, the patient population is originally claimed as
6 “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500
7 mg/dl.”⁹⁴⁷ The asserted claims recite the same patient population. Defendants do not contend
8 that the patient population of the asserted claims is not literally described by the specification
9 and in the original claims of the application to which the asserted patent claims priority. In fact,
10 the specification and the provisional patent application claims at the time of filing describe these
11 limitations.⁹⁴⁸ Therefore, Defendants have failed to explain whether and how an aspect of the
12 claimed invention has not been described with sufficient particularity such that one skilled in the
13 art would recognize that the applicant had possession of the claimed invention.

14 Second, Defendants contend that “a person of skill in the art would not understand that
15 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
16 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
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18

19 ⁹⁴⁵ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
20 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
21 legal foundation for claiming that species.”).

22 ⁹⁴⁶ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
23 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
24 a description of the invention defined by the claims”).

⁹⁴⁷ See ‘727 prosecution history.

⁹⁴⁸ See e.g., ‘727 patent at 13:29-34; 14:49-51; U.S. Provisional Application No. 61/151,291.

1 dosages and quantities of the claimed methods.⁹⁴⁹ Moreover, the dosages and quantities of the
2 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
3 claimed invention is adequately described.⁹⁵⁰ Defendants do not and cannot rebut this
4 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
5 to about 4g.”⁹⁵¹ The asserted claims recite “4 g.” Defendants do not contend that dosages and
6 quantities of the asserted claims are not literally described by the specification and in the original
7 claims. In fact, the specification and the provisional patent application claims, at the time of
8 filing, described these limitations. Therefore, Defendants have failed to explain whether and
9 how an aspect of the claimed invention has not been described with sufficient particularity such
10 that one skilled in the art would recognize that the applicant had possession of the claimed
11 invention.

12 Third, Defendants contend that “a person of skill in the art would not understand that the
13 inventor was in possession of a method comprising a comparison against a second subject or
14 against a second population.” The specification demonstrates that the applicants were in
15 possession of the claimed inventions. For example, a person of ordinary skill would have
16 understood that the inventor was in possession of a method comprising administration of a
17 composition with the recited properties, based on a comparison of a subject or a population
18 against a second subject or a second population.

19 ⁹⁴⁹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
20 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
21 *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

22 ⁹⁵⁰ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
23 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
24 a description of the invention defined by the claims”).

⁹⁵¹ See U.S. Provisional Application No. 61/151,291.

1 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,⁹⁵² the court
2 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
3 specification of asserted patents literally disclose the claimed invention in the specification and
4 the claims as originally filed. Thus, an examination of the four corners of the specification from
5 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
6 asserted patents were in possession of the claimed invention.

7 Defendants conclude by alleging that the specification does not describe anything more
8 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
9 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
10 specification; nonobviousness can be supported by post-filing date evidence for example.⁹⁵³
11 Written description requires only that the specification reasonably conveys that the applicant had
12 possession of the claimed subject matter when the application was filed. Therefore, whether the
13 claims are obvious has no bearing on the adequacy of written description.

14 c) Defendants Have Not Demonstrated that the Claims of the ‘728
15 Patent Are Invalid for Lack of Enablement

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

19 _____
⁹⁵² *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 ⁹⁵³ See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
24 1307 (. 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 (. 2004) (“Evidence
developed after the patent grant is not excluded from consideration, for understanding of the full range of an
invention is not always achieved at the time of filing the patent application.”).

1 Factors that may be considered include the quantity of experimentation necessary, the amount of
2 direction or guidance presented, the presence or absence of working examples, the nature of the
3 invention, the state of the prior art, the relative skill of those in the art, the predictability or
4 unpredictability of the art, and the breadth of the claims.⁹⁵⁴ The enablement requirement is
5 separate and distinct from the written description requirement,⁹⁵⁵ and as such a claim does not
6 require descriptive support in the disclosure as originally filed for it to be enabled.⁹⁵⁶

7 Defendants make three specific arguments regarding the enablement requirement. First,
8 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
9 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
10 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
11 skill would be able to determine the amounts of the components in the pharmaceutical
12 composition without any experimentation, much less undue experimentation.

13 Second, Defendants contend that it would take undue experimentation to obtain the
14 claimed required results listed in the full scope of the patent claims, including the claimed lipid
15 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
16 method and certainly not undue experimentation. Administration of a recited amount of a recited
17 composition, for a recited duration, to a specific, recited patient population produces the recited
18 results. No additional experimentation is required, and Defendants do not explain their
19 allegation that undue experimentation would be required. Defendants also do not contend that
20 following the claimed method (each recited element) does not produce the recited results. The
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22 ⁹⁵⁴ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ⁹⁵⁵ *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ⁹⁵⁶ MPEP § 2164.

1 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
2 demonstrate that administration of EPA of the recited composition, when administered to
3 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
4 results.⁹⁵⁷ Therefore, the claims are not invalid for lack of enablement.

5 Third, Defendants allege that “it would require undue experimentation to obtain the
6 claimed required results in subjects who do ‘not receive concurrent lipid altering therapy’
7 because the patentee did not separately study such subjects.” Yet, as Defendants admit, the
8 example in the specification includes both subjects who did not receive concurrent lipid altering
9 therapy. This is consistent with the prosecution history, which includes a study of both subjects
10 on statins and not on statins.

11 Defendants conclude by alleging that the specification does not enable anything more
12 than what is obvious over the prior art or was known to a person of skill in the art. First,
13 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
14 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
15 precluded in the future from raising any new legal theory to support this assertion. Moreover,
16 while the ’728 patent’s specification enables a person of ordinary skill to obtain the claimed
17 limitations without undue experiment, the claimed limitations would not have been obvious to a
18 person of ordinary skill, as discussed in Section V.A.3. Furthermore, Plaintiffs have initiated
19 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
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23 ⁹⁵⁷ See VASCEPA Prescribing Information at Table 2.
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1 | claimed methods.^{958,959} Therefore, a person of ordinary skill would have concluded that the
2 | claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

3 | **B. The ‘715 Patent**

4 | **1. The ‘715 Patent Claims Eligible Subject Matter Under § 101**

5 | Defendants’ allegation that the asserted claims of the ‘715 patent relate to ineligible
6 | subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
7 | case under Section 101 or provide a legal or factual basis to support their allegations.

8 | As an initial matter, Defendants’ disclosure is also insufficient under the Nevada Local
9 | Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
10 | provided.⁹⁶⁰ The bare assertion of invalidity under Section 101 without providing the grounds
11 | for such an allegation and examining the elements of the asserted claims of the ‘715 patent does
12 | not meet this requirement and thwarts the purpose of the Rules.⁹⁶¹

13 | The inquiry under Section 101 involves a two-step test: first, a court must determine
14 | whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
15 |

16 | ⁹⁵⁸ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
17 | doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
18 | trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
19 | the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

18 | ⁹⁵⁹ See May 16, 2011 Bays Declaration at Appendix B.

19 | ⁹⁶⁰ See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
20 | other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
21 | statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

21 | ⁹⁶¹ Nor does the preceding paragraph, which provides only a purported summary of the claims of the ‘715 patent, or
22 | subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
23 | grounds for Defendants’ allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,*
24 | *Inc. v. Garmin Int’l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

1 phenomenon, or abstract idea.⁹⁶² Second, even if the claim is directed to one of these concepts, it
2 still may be patent eligible and the court must determine what else is part of the claim.⁹⁶³

3 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
4 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
5 the '715 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
6 conventional” steps, and the only novel element related to administering the proper dosage based
7 on a natural law observation.⁹⁶⁴ However, the claims merely recited this natural law without
8 reciting any novel application of it.⁹⁶⁵ The Court found that providing protection to such claims
9 would result in pre-empting “a broad range of potential uses” and excluding others from using
10 “the basic tools of scientific and technical work.”⁹⁶⁶ A method of treatment claim, specifying the
11 subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and
12 instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
13 protection.⁹⁶⁷

14 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
15 occurring substance. It is not. Even references contained within Defendants’ own contentions
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17 ⁹⁶² *Alice Corp. Pty. v. CLS Bank Int’l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
18 issue are directed to one of those patent-ineligible concepts.”).

19 ⁹⁶³ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

20 ⁹⁶⁴ *Mayo*, 132 S. Ct. at 1294.

21 ⁹⁶⁵ *Id.* at 1301.

22 ⁹⁶⁶ *Id.*

23 ⁹⁶⁷ *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
24 of using an existing drug); see also *Diamond v. Diehr*, 450 U.S. 175, 177, 191-193 (1981) (upholding patentability
for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

1 make clear that EPA of the requisite purity and characteristics is not found in nature.⁹⁶⁸ As
2 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
3 decades it has been accepted that compositions isolated from nature or purified beyond their
4 natural state are patent-eligible.⁹⁶⁹ Moreover, Defendants’ assertions are immaterial to a Section
5 101 defense because method of treatment claims like the ones asserted in this case are patent
6 eligible even if they are directed to administration of a naturally occurring substance.⁹⁷⁰

7 To the extent Defendants are arguing that a law of nature both underlies the claims and
8 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
9 claimed effects are the natural result of ingesting a naturally-occurring substance.”⁹⁷¹ Since the
10 composition that is the subject of the claims is not naturally occurring, Defendants appear to
11 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
12 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
13 characterization of laws of nature.⁹⁷² To say that the claims of the ’715 patent claim a law of
14 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
15 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
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17 ⁹⁶⁸ See, e.g., U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
18 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, e.g., at 26–27).

19 ⁹⁶⁹ See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

20 ⁹⁷⁰ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

21 ⁹⁷¹ See Defendants’ Joint Invalidity Contentions at 248.

22 ⁹⁷² See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes to
23 achieve a desired outcome That one way of describing the process is to describe the natural ability of the
24 subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

1 underlying principles of nature” that would “make all inventions unpatentable.”⁹⁷³ Indeed, even
2 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
3 claims not treatment claims of the type that *Mayo* stated were typical and patentable.⁹⁷⁴

4 Even if there is some underlying law of nature in the asserted claims, the subject matter
5 of the '715 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
6 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
7 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
8 foreclose from others the use of that equation in conjunction with all of the other steps in their
9 claimed process.’”⁹⁷⁵ As discussed above, the asserted claims of the '715 patent contain a novel,
10 unconventional, and specific method of treatment comprising a particularized application of a
11 nonnaturally occurring substance and does not preempt the use of a law of nature.⁹⁷⁶

12 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
13 arguments are further evidence of invalidity under § 101. This argument is without merit. The
14 claims are enabled and written description is satisfied for the reasons discussed below. In
15 addition, as discussed above, the asserted claims are not merely a naturally-occurring
16 phenomena, and thus satisfy the requirements of § 101.

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⁹⁷³ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

20 ⁹⁷⁴ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ⁹⁷⁵ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ⁹⁷⁶ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 **2. The Asserted Claims of the ‘715 Patent Are Not Anticipated by WO**
2 **‘118**

3 To anticipate, a single prior art reference must sufficiently describe a claimed invention
4 so that the public is in “possession” of that invention.⁹⁷⁷ Therefore, to anticipate, a reference
5 must set forth every element of the claim, either expressly or inherently, in as complete detail as
6 is contained in the claim.⁹⁷⁸ The claim elements must also be “arranged” in the prior art
7 reference, just as they are in the claim,⁹⁷⁹ rather than as “multiple, distinct teachings that the
8 artisan might somehow combine to achieve the claimed invention.”⁹⁸⁰ In addition, public
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the
10 invention without undue experimentation.⁹⁸¹ Factors that may be included in this analysis
11 include the quantity of experimentation necessary, the amount of direction or guidance
12 presented, the presence or absence of working examples, the nature of the invention, the state of
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
14 and the breadth of the claims.⁹⁸² This inquiry is objective, and thus evidence of undue
15 experimentation need not be prior art.⁹⁸³

16 _____
⁹⁷⁷ *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 ⁹⁷⁸ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
18 Cir. 1989).

⁹⁷⁹ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 ⁹⁸⁰ *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
(C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

20 ⁹⁸¹ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,*
21 *Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

⁹⁸² *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 ⁹⁸³ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999 F.2d
23 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
24 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-19 of the '715 Patent are anticipated by the WO '118
2 reference.⁹⁸⁴

3 A element-by-element analysis, identifying each element of each asserted claim that is
4 absent from WO '118, is provided below. The contentions below are incorporated by reference
5 into Exhibit B, and vice-versa. WO '118 does not anticipate the claims of the '715 patent
6 because it does not describe, properly arrange, or enable the '715 patent claims.

7 a) WO '118 Does Not Teach Every Element of the Claims of the
8 '715 Patent

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

10 It is well established that, for a prior art reference to anticipate, “every element of the
11 claimed invention must be identically shown in a single reference.”⁹⁸⁵ Moreover, the elements of
12 the claimed invention must have “strict identity” with the elements of the reference; “minimal
13 and obvious” differences are sufficient to prevent anticipation.⁹⁸⁶ Here, WO '118 entirely fails to
14 disclose the following elements of Claim 1 of the '715 Patent: *to effect a reduction in*
15 *triglycerides and apolipoprotein B in the subject compared to a triglyceride level and*
16 *apolipoprotein B level in a second subject having a fasting baseline triglyceride level of 500*
17 *mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, and who*
18 *has not received the pharmaceutical composition.* WO '118 entirely fails to disclose the
19 following elements of Claim 13 of the '715 Patent: *to effect a statistically significant reduction*
20 *in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein*

21 _____
22 ⁹⁸⁴ 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.

23 ⁹⁸⁵ *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).

24 ⁹⁸⁶ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 *B in the subject.* WO '118 entirely fails to disclose the following elements of Claim 17 of the
2 '715 Patent: *to effect reduction in triglycerides and apolipoprotein B in the subject compared to*
3 *a triglyceride level and an apolipoprotein B level at a baseline prior to initial administration of*
4 *the pharmaceutical composition.* Defendants appear to concede that WO '118 does not
5 expressly teach these elements, as they fail to set forth any basis for concluding that WO '118
6 teaches this element.⁹⁸⁷ Indeed, Defendants could not set forth any basis for concluding that WO
7 '118 teaches this element because WO '118 does not.

8 Instead, Defendants argue that these elements express the intended result of a method that
9 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
10 below, WO '118 fails to disclose each element of the independent claims of the '715 Patent,
11 either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method.

12 Defendants also argue that these elements represent inherent, natural properties of EPA, and are
13 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of
14 anticipation and claim construction. Further, while Defendants argue that the inherent properties
15 are exemplified in the prior art, they fail to identify even a single prior art reference that makes
16 such a disclosure. Defendants cannot point to a single, specific prior art reference because the
17 claimed pharmaceutical composition has never been administered in the manner claimed to the
18 claimed patient population. Also, these elements are positively recited in the body of the claim
19 and therefore cannot be construed as a non-limiting preamble and must be given patentable
20 weight.

21 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
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24 ⁹⁸⁷ Defendants' Invalidity Contentions at 202-204.

1 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
2 inherently anticipate as a matter of law.”⁹⁸⁸ “[A]nticipation by inherent disclosure is appropriate
3 only when the reference discloses prior art that must *necessarily* include the unstated
4 limitation.”⁹⁸⁹ “It is not sufficient if a material element or limitation is ‘merely probably or
5 possibly present’ in the prior art.”⁹⁹⁰ WO ‘118 fails to provide any data related to the lipid
6 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
7 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets
8 the elements of the independent claims every time it is administered.

9 Defendants fail to demonstrate that administration of the claimed EPA compositions
10 “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants
11 suggests that EPA administration may increase LDL-C.⁹⁹¹ Rambjor is a clinical study which
12 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
13 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
14 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
15 decrease TG without increasing LDL-C *every time it is administered*.

16 Therefore, WO ‘118 cannot anticipate the independent claims of the ‘715 patent.
17 Because the dependent claims include all of the claim elements of the independent claims, WO’
18 118 cannot anticipate any of the dependent claims as well.

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22 ⁹⁸⁸ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ⁹⁸⁹ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ⁹⁹⁰ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

⁹⁹¹ *See, e.g.*, Rambjor.

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

3 In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition
4 be administered in the manner claimed to the claimed patient population. Defendants attempt to
5 eliminate these important elements by arguing that the preamble is non-limiting. A preamble is
6 the introductory clause of a patent claim and includes everything from the beginning of the claim
7 until a transitional phrase, such as “comprising.” Defendants improperly attempt to truncate the
8 preamble.

9 A claim preamble has patentable weight if, “when read in the context of the entire claim,
10 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,
11 and vitality’ to the claim.”⁹⁹² Additionally, the preamble constitutes a claim element when the
12 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
13 claim body to define the claimed limitation.”⁹⁹³

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

18 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
19 properly construed as a limitation of the claim itself.”⁹⁹⁴ The recitation of a “method of reducing

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21 ⁹⁹² *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

22 ⁹⁹³ *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

23 ⁹⁹⁴ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer Docking*
24 *Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases “portable
computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

1 triglycerides” in the preamble provides antecedent basis for the effect of reducing triglycerides in
2 the body of the claim and emphasizes the intentional purpose for which the method must be
3 performed - to reduce triglycerides.

4 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
5 to define the subject matter of the claimed invention.”⁹⁹⁵ Thus, the entire preamble in the
6 independent claims of the ‘715 must contain patentable weight.

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

10 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
11 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**
12 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
13 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
14 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and
15 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
16 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
17 angina and exercise-induced angina, and destabilization of the angina.”⁹⁹⁶ The invention of WO
18 ‘118 is intended to be administered to any person in need of prevention of the occurrence of
19 cardiovascular events, who are typically hypercholesterolemia patients.⁹⁹⁷ WO ‘118 does not
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⁹⁹⁵ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

23 ⁹⁹⁶ WO ‘118 at 12.

24 ⁹⁹⁷ *Id.*

1 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
2 anticipate the independent claims.

3 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail
4 to prove that these elements of the claimed invention have “strict identity” with the elements of
5 the reference.⁹⁹⁸ WO ‘118 fails to anticipate this claim element because the broad disclosure
6 fails to anticipate the narrow claimed range, and the specific patient population defined in the
7 claims is an essential part of the claimed invention.

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

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24 ⁹⁹⁸ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 used in the over 500 mg/dL TG patient population. A prior art reference that “only ‘probably’ or
2 ‘possibly’ meets the claims cannot inherently anticipate as a matter of law.”⁹⁹⁹ Therefore,
3 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
4 ‘118 meets the claim elements of the independent claims every time it is administered.

5 Further, the broad range disclosed by WO ‘118 is insufficient to anticipate the ranges
6 claimed by the ‘715 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
7 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
8 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
9 claimed temperature range, “[g]iven the considerable difference between the claimed range and
10 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
11 claimed range with sufficient specificity to anticipate this element of the claim.”¹⁰⁰⁰ A prior art’s
12 teaching of a broad genus does not necessarily disclose every species within that genus. The
13 court explained the slightly overlapping range between the preferred range and claimed range “is
14 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”¹⁰⁰¹ and therefore
15 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
16 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
17 anticipate the subject as described in the claims because it fails to described the claimed TG
18 range with sufficient specificity.

19 The court in *Atofina* ruled on an additional question of anticipation that also involved a
20 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

22 ⁹⁹⁹ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ¹⁰⁰⁰ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

24 ¹⁰⁰¹ *Atofina*, 441 F.3d at 1000.

1 compared to the patent’s claimed range of 0.1 to 5.0 percent.¹⁰⁰² The court explained that
2 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
3 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
4 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”¹⁰⁰³ Similarly,
5 although there may be overlap between the definition of hypertriglyceridemia taught by WO
6 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
7 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500
8 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of
9 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
10 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
11 events as the primary clinical objective),¹⁰⁰⁴ WO ‘118, therefore, does not expressly disclose the
12 specific patient population that is an essential element of the claims of the asserted patents.
13 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

14 The treatment of a patient with elevated TG levels varies depending on their serum
15 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
16 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
17 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
18 of lipid disorders.¹⁰⁰⁵ The ATP-III divided hypertriglyceridemia patients into three classes based
19 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
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21 ¹⁰⁰² *Id.*

22 ¹⁰⁰³ *Id.*

23 ¹⁰⁰⁴ *See* Section III.

24 ¹⁰⁰⁵ *Id.*

1 and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment
2 strategies for patients depending on classification.¹⁰⁰⁶ For the borderline-high and high TG
3 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.¹⁰⁰⁷
4 Accordingly, in these populations, physicians focused on lowering LDL-C.¹⁰⁰⁸ In this patient
5 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
6 In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of
7 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated
8 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
9 treatment goal.¹⁰⁰⁹ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
10 were considered fundamentally different from patients with borderline-high or high TGs from a
11 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

12 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
13 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
14 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
15 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
16 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
17 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels
18 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
19 decreasing triglycerides), as required by the independent claims of the asserted patents, and
20 therefore cannot anticipate the independent claims of the ‘715 Patent.

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22 ¹⁰⁰⁶ ATP III at 3335; *See also* Section III.

23 ¹⁰⁰⁷ *Id.*

24 ¹⁰⁰⁸ *Id.*

¹⁰⁰⁹ *Id.*

1 Third, WO '118 fails to disclose the claim element of "a subject . . . who does not receive
2 a concurrent lipid altering therapy." Defendants' only basis for concluding that WO '118
3 teaches this element is that WO '118 "discloses and claims the administration of EPA-E without
4 the administration in combination with statins."¹⁰¹⁰ This sentence appears to be incomplete, as it
5 is unclear what Defendants mean by "without the administration in combination with statins."
6 This single statement, without citation to a single page in WO '118, fails to demonstrate that WO
7 '118 teaches this element. In fact, WO '118 methods comprise statins, i.e. HMG-CoA RI.¹⁰¹¹

8 WO '118 states that its disclosed composition is "effective in preventing occurrence of
9 cardiovascular events in hypercholesterolemia patients, and **in particular**, in preventing
10 occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with
11 HMG-CoA RI but still suffer from the risk of the cardiovascular events."¹⁰¹² WO '118 goes on
12 to state that the "effect of the composition of the present invention will be synergistically
13 improved by combined use with the HMG-CoA RI, and such use of the composition of the
14 present invention with the HMG-CoA RI has clinical utility since the effect of preventing the
15 cardiovascular event occurrence is expected to be improved."¹⁰¹³ Administering the composition
16 of WO '118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-
17 CoA RI has on the disclosed compound. Further, WO '118 teaches that the disclosed
18 composition may be used with a long list of other drugs, including lipid altering drugs such as
19 antilipotropic drugs and fibrate drugs.¹⁰¹⁴ Thus, WO '118 does not disclose administration of the

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21 ¹⁰¹⁰ Defendants' Invalidity Contentions at 46.

22 ¹⁰¹¹ HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of
23 drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

24 ¹⁰¹² WO '118 at 9 (emphasis added).

¹⁰¹³ *Id.* at 10.

¹⁰¹⁴ *Id.* at 24-25.

1 claimed EPA compositions to a subject that has very high TG levels and also “does not receive a
2 concurrent lipid altering therapy” and cannot anticipate the independent claims of the ‘715
3 patent. In fact, the example of the methods of WO ‘118 expressly teaches a statin/EPA co-
4 therapy. Because the dependent claims depend from the independent claims, they include the
5 elements of the independent claims. Thus, WO ‘118 cannot anticipate any of the dependent
6 claims of the ‘715 patent.

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

9 WO ‘118 further does not anticipate the claims of the ‘715 patent because it does not
10 disclose “administering orally to the subject.” As WO ‘118 fails to disclose the subject as
11 claimed, it cannot anticipate oral administration to the claimed “subject.”

12 WO ‘118 additionally cannot anticipate the claims of the ‘715 patent because it does not
13 disclose administering the pharmaceutical composition at a dose of about 4g per day.
14 Defendants argue that this element is disclosed by WO ‘118’s teaching that the daily dose is
15 “typically 0.3 to 6 g/day.” Defendants fail to provide the entire disclosure of WO ‘118, which
16 states that the daily dose is “typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more
17 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
18 g.day. Another preferable fatty acid included is DHA-E.” WO ‘118 teaches that the dosage is
19 not particularly limited as long as the intended effect, preventing the occurrence of
20 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
21 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
22 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
23 working examples, data or other reference in WO ‘118 indicating that any subject (much less
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1 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
2 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

3 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
4 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
5 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic
6 range of 330 to 450 °C,”¹⁰¹⁵ and therefore failed to anticipate the claimed range. The court in
7 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
8 the patent’s claimed range of 0.1 to 5.0 percent.¹⁰¹⁶ The court explained that “although there is a
9 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
10 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
11 different, not the same. . . . Thus, there is no anticipation.”¹⁰¹⁷ Similarly, although there may be
12 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘715
13 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range
14 claimed by the ‘715 patent does not fall within WO ‘118’s preferred range. Defendants
15 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,
16 the example indicates that up to 900 mg of the EPA composition could be used three times per
17 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘715
18 patent and cannot anticipate the independent claims of the ‘715 Patent.

19 WO ‘118 further does not anticipate the claims of the ‘715 patent because it does not
20 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
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¹⁰¹⁵ *Atofina*, 441 F.3d at 1000.

23 ¹⁰¹⁶ *Id.*

24 ¹⁰¹⁷ *Id.*

1 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.
2 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high
3 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
4 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
5 higher, and still more preferably 96.5% by weight or higher.”¹⁰¹⁸ Therefore, WO ‘118 discloses
6 EPA-E with “high purity” is a composition which contains EPA-E of 40% by weight, of total
7 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
8 generic range for the EPA composition in the claimed pharmaceutical composition.

9 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the
10 . . . range claimed in the” patent is insufficient for anticipation.¹⁰¹⁹ In *Atofina*, the prior art
11 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
12 range between 330 and 450 degrees. The court explained that this slight overlap “is not
13 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”¹⁰²⁰ and therefore failed
14 to anticipate the claimed range.¹⁰²¹ The court in *Atofina* also found that a prior art disclosure of a
15 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
16 percent.¹⁰²² The court explained that “although there is a slight overlap, no reasonable fact finder
17 could determine that this overlap describes the entire claimed range with sufficient specificity to
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21 ¹⁰¹⁸ WO ‘118 at 22.

22 ¹⁰¹⁹ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

23 ¹⁰²⁰ *Atofina*, 441 F.3d at 1000.

24 ¹⁰²¹ *Atofina*, 441 F.3d at 1000.

¹⁰²² *Id.*

1 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
2 anticipation.”¹⁰²³

3 Similarly, although there may be some overlap between the E-EPA content disclosed by
4 WO ‘118 and the ranges claimed by the ‘715 patent, WO ‘118 does not specifically highlight the
5 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
6 critical factor of the invention disclosed in the ‘715 patent. Therefore, WO ‘118’s broad
7 disclosure of the E-EPA content in its invention does not describe the claimed range with
8 sufficient specificity and cannot anticipate the independent claims of the ‘715 patent.

9 WO ‘118 is additionally insufficient for anticipation because it does not expressly
10 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118
11 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is
12 DHA-E.”¹⁰²⁴ The disclosure goes on to state that the composition of the invention is preferably
13 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
14 pharmaceutical composition is a critical factor of the invention disclosed in the ‘715 patent.

15 The disclosure of WO ‘118 treats DHA and EPA interchangeably. The disclosed
16 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
17 There is no express teaching or guidance directing the person of ordinary skill in the art to the
18 claimed EPA compositions, Therefore, WO ‘118’s broad disclosure, which indicates no
19 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
20 claims of the ‘715 patent.

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¹⁰²³ *Id.*

24 ¹⁰²⁴ WO ‘118 at 22.

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

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

18 (4) WO ‘118 Does Not Describe the Dependent Claims

19 Defendants fail to address any of the claim elements of the dependent claims.
20 Defendants appear to concede that WO ‘118 does not expressly teach these elements, as they fail
21 to set forth any meaningful basis for concluding that WO ‘118 teaches these elements.
22 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by
23 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
24 no patentable weight.” To the extent the recited claim elements relate to the administration step,

1 the dosage form or characteristics of the treated subject and the specific effect produced by the
2 claimed method, Defendants’ contentions that the claim limitations are inherent properties of
3 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
4 ‘118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
5 Defendants have not met the burden to establish anticipation with the naked assertion that the
6 effects are inherent, natural properties of EPA.

7 Further, Defendants entirely fail to prove that inherently discloses the recited claim
8 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
9 inherently anticipate as a matter of law.”¹⁰²⁵ “[A]nticipation by inherent disclosure is appropriate
10 only when the reference discloses prior art that must *necessarily* include the unstated
11 limitation.”¹⁰²⁶ “It is not sufficient if a material element or limitation is ‘merely probably or
12 possibly present’ in the prior art.”¹⁰²⁷ Defendants fail to show that WO ‘118 “*necessarily*” meets
13 the recited claim elements relating to the administration step, the dosage form or characteristics
14 of the treated subject and the specific effect produced by the claimed method *every time*. WO
15 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
16 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
17 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,
18 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
19 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim
20 elements.

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22 ¹⁰²⁵ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ¹⁰²⁶ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ¹⁰²⁷ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
2 further in view of Nozaki and/or Hayashi and further in view of Grimsgaard, Mori
2000 and/or Maki.”

- 3 • 3) “. . . the asserted claims of the ’715 patent would have been obvious over Omacor
4 PDR/Lovaza PDR in combination with the known clinical benefits of administering
5 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or
6 Shinozaki in further view of Contacos.
- 7 • 4) “. . . the asserted claims of the ’715 patent would have been obvious over WO ’118
8 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the
9 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 10 • 5) “. . . the asserted claims of the ’715 patent would have been obvious over WO
11 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
12 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
13 further in view of Katayama, Matsuzawa and/or Takaku.”

14 A patent claim is invalid “if the differences between the subject matter sought to be
15 patented and the prior art are such that the subject matter as a whole would have been obvious at
16 the time the invention was made to a person having ordinary skill in the art.”¹⁰³¹ Obviousness is
17 a legal determination, but it turns on factual inquiries into (1) the level of ordinary skill in the art,
18 (2) the scope and content of the prior art, and (3) the differences between the prior art and the
19 claims at issue.¹⁰³²

20 In evaluating obviousness, each prior art reference must be evaluated for all that it
21 teaches, including the portions that would lead away from the claimed invention.¹⁰³³ Indeed, any
22 teaching in the art that points away from the claimed invention must be considered.¹⁰³⁴ A
23 reference teaches away if a person of ordinary skill, upon reading the reference, would be
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21 ¹⁰³¹ 35 U.S.C. § 103(a).

22 ¹⁰³² *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

23 ¹⁰³³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ¹⁰³⁴ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

1 discouraged from following the path set out in the reference, or would be led in a direction
2 divergent from the path that was taken by the applicant.¹⁰³⁵ For instance, a reference teaches
3 away if it suggests that the line of development flowing from the reference’s disclosure is
4 unlikely to be productive of the result sought by the applicant.¹⁰³⁶

5 In order to find obviousness based on a combination of references, there must be some
6 rationale for combining the references in the way claimed that is separate and apart from the
7 hindsight provided by the patented invention itself.¹⁰³⁷ The law prohibits an obviousness
8 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
9 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
10 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
11 invention.”¹⁰³⁸ “The invention must be viewed not after the blueprint has been drawn by the
12 inventor, but as it would have been perceived in the state of the art that existed at the time the
13 invention was made.”¹⁰³⁹

14 “The determination of obviousness is made with respect to the subject matter as a whole,
15 not separate pieces of the claim.”¹⁰⁴⁰ “[A] patent composed of several elements is not proved
16 obvious merely by demonstrating that each of its elements was, independently, known in the
17 prior art.”¹⁰⁴¹ “This is so because inventions in most, if not all, instances rely upon building

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19 ¹⁰³⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

20 ¹⁰³⁶ *Id.*

21 ¹⁰³⁷ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

22 ¹⁰³⁸ *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

23 ¹⁰³⁹ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

24 ¹⁰⁴⁰ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

¹⁰⁴¹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

1 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
2 of what, in some sense, is already known.”¹⁰⁴²

3 Accordingly, it is improper to pick and choose isolated elements from the prior art and
4 combine them so as to yield the invention¹⁰⁴³ or to modify a prior art reference in a way that
5 “would destroy the fundamental characteristics of that reference.”¹⁰⁴⁴ Moreover, a combination
6 is not obvious where “it would be impossible to apply these teachings [of the secondary
7 reference] to the [primary reference] without entirely changing the basic mechanism and
8 procedure thereof,”¹⁰⁴⁵ or where the proposed combination requires “material and radical
9 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
10 prior art device.¹⁰⁴⁶ Furthermore, it is improper “to modify the secondary reference before it is
11 employed to modify the primary reference” in assessing obviousness.¹⁰⁴⁷

12 Further, a party asserting obviousness in view of a combination of prior art disclosures
13 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
14 combine the elements in the manner claimed¹⁰⁴⁸ and “a reasonable expectation of success.”¹⁰⁴⁹

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16 ¹⁰⁴² *KSR*, 550 U.S. at 418-419.

17 ¹⁰⁴³ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

18 ¹⁰⁴⁴ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

19 ¹⁰⁴⁵ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

20 ¹⁰⁴⁶ *Id.* at 88.

21 ¹⁰⁴⁷ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

22 ¹⁰⁴⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
23 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
24 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

¹⁰⁴⁹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 For chemical compounds, there must have been a reason both to select the prior art
2 compound “most promising to modify” and to make the necessary changes to arrive at the
3 claimed compound.¹⁰⁵⁰ This protects against the use of hindsight to pick through the prior art
4 based solely on structural similarity to the claimed compound.¹⁰⁵¹ Any assertion of an “apparent
5 reason” must find a basis in the factual record.¹⁰⁵²

6 The “reasonable expectation of success” for a chemical compound must be of all of a
7 claimed compound’s relevant properties,¹⁰⁵³ including those discovered after the patent was filed
8 or even issued.¹⁰⁵⁴ “The basic principle behind this rule is straight-forward—that which would
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10 ¹⁰⁵⁰ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
11 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli
Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

12 ¹⁰⁵¹ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
13 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
2002).

14 ¹⁰⁵² *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
16 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
17 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
18 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
19 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”).

20 ¹⁰⁵³ *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. . .
21 . [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
22 820, 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.”).

23 ¹⁰⁵⁴ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
24 908.

1 have been surprising to a person of ordinary skill in a particular art would not have been
2 obvious.”¹⁰⁵⁵ Any assertion of a “reasonable expectation of success” must find a basis in the
3 factual record.¹⁰⁵⁶

4 In an obviousness determination, any objective indicia of nonobviousness must be taken
5 into account.¹⁰⁵⁷ An objective indicium is any “event[] proved to have actually happened in the
6 real world” that evidences the nonobvious nature of the invention.¹⁰⁵⁸ The existence of an
7 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
8 surprising results, expressions of skepticism, industry praise, commercial success, and copying
9 are classical indicia of nonobviousness.¹⁰⁵⁹ These factual inquiries “guard against slipping into
10 use of hindsight,”¹⁰⁶⁰ and “may often be the most probative and cogent evidence of
11 nonobviousness.”¹⁰⁶¹

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14 ¹⁰⁵⁵ *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results.”).

15 ¹⁰⁵⁶ 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.’”).

17 ¹⁰⁵⁷ *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).

18 ¹⁰⁵⁸ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

19 ¹⁰⁵⁹ *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.

21 ¹⁰⁶⁰ *Graham*, 383 U.S. at 36.

22 ¹⁰⁶¹ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting Inc. v. Lampro Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

1 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
2 have been fully “in possession” of the public—which requires that the claimed invention have
3 been enabled.¹⁰⁶²

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

7 a) General Overview

8 Defendants fail to provide a single prior art reference that discloses administration of the
9 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
10 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
11 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
12 concentrations, in a wide range of doses and administration periods, to subjects who have
13 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
14 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
15 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
16 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
17 distinguish between the effect of the placebo from that of the active agent. Studies which
18 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
19 independent effects of EPA and DHA.¹⁰⁶³ Inconsistency in dosages and administration periods

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21 ¹⁰⁶² *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
22 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
23 making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
24 itself is in the possession of the public.”).

¹⁰⁶³ *Mori* 2006 at 96.

1 and variations in the administered fatty acid compositions also complicate the interpretation of
2 the results and limit the application of these studies.

3 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
4 very high TGs together with patients with high and borderline high TGs indicates that there is no
5 medical difference in responsiveness to treatment among the groups of people.”¹⁰⁶⁴ Defendants
6 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
7 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
8 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
9 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
10 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
11 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
12 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.¹⁰⁶⁵ In
13 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
14 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
15 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
16 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
17 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
18 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
19 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical
20 difference in responsiveness to treatment between the very-high TG patient population and lower

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22 ¹⁰⁶⁴ Defendants’ Joint Invalidity Contentions at 260 (*see n.36*).

23 ¹⁰⁶⁵ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
24 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

1 TG patient populations merely because there was possibly one patient with baseline TG levels of
2 at least 500 mg/dL.

3 As discussed above in Section III, patients with very-high TG levels were considered
4 fundamentally different from patients with borderline-high or high TGs from a clinical,
5 regulatory, and therapeutic perspective.¹⁰⁶⁶ Clinically, the authoritative guidance to physicians
6 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
7 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
8 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
9 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
10 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
11 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for
12 very-high TG patients was TG reduction. This distinction between patients with borderline-
13 high/high TG levels and patients with very high TG levels is also observed on the regulatory
14 level. The FDA recognized the different clinical status of the very-high TG population by
15 approving some drugs specifically for the very-high TG group without granting treatment
16 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).¹⁰⁶⁷

17 Finally, from a therapeutic standpoint, a person of ordinary skill understood that the
18 effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the
19 patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known
20 classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the
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23 ¹⁰⁶⁶ See Bays Jan. 8, 2012 Decl., ¶ 20.

24 ¹⁰⁶⁷ See Bays Jan. 8, 2012 Decl., ¶ 22.

1 invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG
2 level of the patient receiving treatment.

3 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
4 *increase* LDL-C in very-high TG patients.¹⁰⁶⁸ The fibrate, Tricor (fenofibrate), for example,
5 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)¹⁰⁶⁹
6 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).¹⁰⁷⁰ In
7 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
8 significant increase in LDL-C was observed.¹⁰⁷¹ In patients with very-high TGs (mean baseline
9 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).¹⁰⁷² Similar
10 results were seen with the administration of Lopid (gemfibrozil).¹⁰⁷³ The differing effects of
11 fibrates, such as Tricor, on TG, LDL-C, HDL-C and Total-C based on baseline TG values
12 demonstrates how a person of ordinary skill at the time of the invention would have understood
13 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
14 parameters in patients with normal, borderline-high or high TG levels would be the same in
15 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
16 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with

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19 ¹⁰⁶⁸ 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).

¹⁰⁶⁹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

20 ¹⁰⁷⁰ *Id.*

21 ¹⁰⁷¹ *Id.* See also, Trilipix Label at 27.

22 ¹⁰⁷² *Id.* See also, Trilipix Label at 27.

23 ¹⁰⁷³ 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).

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1 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 2 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 3 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 4 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ¹⁰⁷⁴	101.7 mg/dL	-23.5%*	-31.4%*	+9.8%*	-22.4%*
	231.9 mg/dL	-35.9%*	-20.1%*	+14.6%*	-16.8%*
	432 mg/dL	-46.2*	+14.5	+19.6*	-9.1*
	726 mg/dL	-54.5*	+45.0*	+22.9*	-13.8*

* = p < 0.05 vs. Placebo

11 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing
 12 lipid effects depending on the patient’s baseline TG level. When administered to patients with
 13 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-
 14 C.¹⁰⁷⁵ It had no significant effect on other lipid-related variable, including LDL-C and Apo-
 15 B.¹⁰⁷⁶ However, when administered to patients with very-high baseline TG levels, TGs were
 16 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.¹⁰⁷⁷
 17 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of
 18 Lovaza/Omacor was beneficial.¹⁰⁷⁸

19 ¹⁰⁷⁴ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

20 ¹⁰⁷⁵ Chan 2002 I at 2379-81.

21 ¹⁰⁷⁶ *Id.*; See also, Westphal at 918.

22 ¹⁰⁷⁷ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

23 ¹⁰⁷⁸ 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
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1 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
2 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
3 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
4 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
5 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
6 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
7 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
8 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
9 VLDL particle conversion.¹⁰⁷⁹ Because normal to high TG patients did not have the large
10 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
11 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
12 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
13 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the

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15 one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity],
16 serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely
17 raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic
18 light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was
19 substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not
20 be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe
21 hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the
22 long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm
23 or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular
24 risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty
acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C
levels (TC minus HDL-C.”)

1079 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.”).

1 highest baseline TG levels¹⁰⁸⁰ and did not increase for patients with lower TG levels. Therefore,
2 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
3 borderline-high or high TG patients was *expected*.

4 Defendants contend that “a composition and its properties are inseparable, and therefore
5 do not impart any additional patentability,” and that “all of the limitations regarding the
6 properties of the ethyl EPA compound identified in the claims of the ‘715 patent are inherent to
7 the compound when administered to a human subject.”¹⁰⁸¹ Inherency may not supply a missing
8 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
9 of ordinary skill in the art.¹⁰⁸² Obviousness is based on what is *known* in the art at the time of the
10 invention.¹⁰⁸³ It was not known or reasonably expected at the time of the claimed invention that
11 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
12 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and
13 Apo-B necessarily present, or the natural result of the combination of elements explicitly
14 disclosed by the prior art.¹⁰⁸⁴ Therefore, inherency does not supply the missing claim elements
15 in the prior art cited by Defendants.

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18 ¹⁰⁸⁰ Bays 2008 I at 400-402.

19 ¹⁰⁸¹ Defendants’ Joint Invalidity Contentions at 261.

20 ¹⁰⁸² See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
21 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
22 obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
23 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
24 fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

¹⁰⁸³ *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.”).

¹⁰⁸⁴ See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

1 Defendants argue that the claims of the ‘715 patent which contain “a limiting clause, such
2 as ‘to effect’ or ‘effecting,’” simply express the intended result of a process step positively
3 recited and therefore are not elements.¹⁰⁸⁵ This is incorrect. “There is nothing inherently wrong
4 with defining some part of an invention in functional terms.”¹⁰⁸⁶ When a clause “states a
5 condition that is material to patentability, it cannot be ignored in order to change the substance of
6 the invention.”¹⁰⁸⁷ The claim term “to effect” acts as a positive claim element if the term
7 represents “unexpected and improved effects of administration of the claimed compound.”¹⁰⁸⁸ In
8 addition, the elements represent unexpected and improved effects of administration of purified
9 EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-
10 C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia.
11 Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must
12 be accorded patentable weight.

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

15 Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent.
16 Where a limitation is absent from any Independent Claim, that limitation is absent from all
17 asserted claims, and that analysis is incorporated by reference into each dependent claim. For
18 any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted
19 claims is not a concession that such limitation is present in the reference. By discussing
20

21 ¹⁰⁸⁵ Defendants’ Joint Invalidation Contentions at 262.

22 ¹⁰⁸⁶ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

23 ¹⁰⁸⁷ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

24 ¹⁰⁸⁸ *AstraZeneca AB v. Dr. Reddy’s Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11–12 (D.N.J. May 18, 2010).

1 Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants
2 have appropriately divided the claim language for any purpose.

3 (1) WO '118

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

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
7 '118 disclose or suggest elements of the '715 Claims. The cited portions of WO '118 do not
8 disclose or suggest these elements at least because they do not disclose or suggest administration
9 of EPA with the recited purity to a subject with the recited very high TG levels who does not
10 receive concurrent lipid altering therapy. The cited portions of WO '118 further do not disclose
11 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
12 dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect a
13 statistically significant reduction in TG without effecting a statistically significant increase in
14 LDL-C or Apo-B in the subject.

15 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
16 claims), WO '118 does not disclose or suggest a subject with the recited very high TG levels
17 who does not receive concurrent lipid altering therapy. WO '118 also does not disclose or
18 suggest the claimed pharmaceutical composition with the recited fatty acids compositions or
19 dosage. With respect to Claim 13, WO '118 further does not disclose or suggest a method to
20 effect a statistically significant reduction in TG without effecting a statistically significant
21 increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, WO '118 further
22 does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject
23 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

1 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
2 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
3 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl compared to the
4 second subject. With respect to Claim 14, this reference fails to disclose or suggest a method to
5 effect a statistically significant reduction in TG and Apo-B without effecting a statistically
6 significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims
7 11, 15, and 18, this reference fails to disclose or suggest the subject consume a Western diet.
8 With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride,
9 non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG
10 levels based on a comparison to the second subject.

11 (2) WO '900

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

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
14 '900 disclose or suggest elements of the '715 Claims. The cited portions of WO '900 do not
15 disclose or suggest these elements at least because they do not disclose or suggest administration
16 of EPA with the recited purity to a subject with the recited very high TG levels who does not
17 receive concurrent lipid altering therapy. The cited portions of WO '900 further do not disclose
18 or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited
19 portions of WO '900 further do not disclose or suggest a method to effect a statistically
20 significant reduction in TG without effecting a statistically significant increase in LDL-C or
21 Apo-B in the subject.

22 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
23 claims), WO '900 does not disclose or suggest a subject with the recited very high TG levels
24 who does not receive concurrent lipid altering therapy. WO '900 also does not disclose or

1 suggest the claimed pharmaceutical composition with the recited fatty acid dosage. With respect
2 to Claim 13, WO '900 further does not disclose or suggest a method to effect a statistically
3 significant reduction in TG without effecting a statistically significant increase in LDL-C or
4 Apo-B in the subject. With respect to Claims 1 and 17, WO '900 further does not disclose or
5 suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting
6 baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

7 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
8 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
9 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl compared to the
10 second subject. With respect to Claim 14, this reference fails to disclose or suggest a method to
11 effect a statistically significant reduction in TG and Apo-B without effecting a statistically
12 significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims
13 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume
14 a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the
15 recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with
16 the claimed TG levels based on a comparison to the second subject.

17 (3) Contacos

18 Contacos describes a study designed to determine the safety and efficacy of a statin
19 (pravastatin) combined with fish oil either alone or in combination, for the management of
20 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in
21 the claims.

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
23 Contacos disclose or suggest elements of the '715 Claims. The cited portions of Contacos do not
24 disclose or suggest these elements at least because they do not disclose or suggest administration

1 of EPA with the recited purity to a subject with the recited very high TG levels who does not
2 receive concurrent lipid altering therapy. The cited portions of Contacos further do not disclose
3 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,
4 dosage, or administration period. The cited portions of Contacos further do not disclose or
5 suggest a method of administering the claimed pharmaceutical composition to effect a
6 statistically significant reduction in TG without effecting a statistically significant increase in
7 LDL-C or Apo-B in the subject.

8 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
9 claims), Contacos does not disclose or suggest a subject with the recited very high TG levels
10 who does not receive concurrent lipid altering therapy. Contacos does not disclose or suggest the
11 claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
12 administration period. With respect to Claim 13, Contacos further does not disclose or suggest a
13 method of administering the claimed pharmaceutical composition to effect a statistically
14 significant reduction in TG without effecting a statistically significant increase in LDL-C or
15 Apo-B in the subject. With respect to Claims 1 and 17, Contacos further does not disclose or
16 suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting
17 baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

18 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
19 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
20 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
21 Claim 14, this reference fails to disclose or suggest the administration of the claimed
22 pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B
23 without effecting a statistically significant increase in LDL-C in the subject. With respect to
24

1 Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject
2 consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest
3 the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject
4 with the claimed TG levels based on a comparison to the second subject.

5 (4) Grimsgaard

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

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
11 Grimsgaard disclose or suggest elements of the ‘715 Claims. The cited portions of Grimsgaard
12 do not disclose or suggest these elements at least because they do not disclose or suggest
13 administration of EPA with the recited purity to a subject with the recited very high TG levels
14 who does not receive concurrent lipid altering therapy. The cited portions of Grimsgaard further
15 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
16 compositions or administration period. The cited portions of Grimsgaard further do not disclose
17 or suggest a method to effect a statistically significant reduction in TG without effecting a
18 statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

19 With respect to Claims 1, 13, and 17 of the ‘715 Patent (and therefore all asserted
20 claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG levels
21 who does not receive concurrent lipid altering therapy. Grimsgaard also does not disclose or
22 suggest the claimed pharmaceutical composition with the recited fatty acids compositions or
23 administration period. With respect to Claim 13, Grimsgaard further does not disclose or suggest
24 a method to effect a statistically significant reduction in TG without effecting a statistically

1 significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect
2 to Claims 1 and 17, Grimsgaard further does not disclose or suggest a method of reducing
3 triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500
4 mg/dl to about 1500 mg/dl.

5 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
6 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
7 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
8 Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant
9 reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the
10 subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to
11 disclose or suggest the subject and second subject consume a Western diet. With respect to
12 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
13 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
14 comparison to the second subject.

15 (5) Hayashi

16 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
17 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
18 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygcleride
19 concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220
20 mg/dl.

21 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
22 ‘715 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
23 administration of EPA with the recited purity to a subject with the recited very high TG levels
24 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject

1 had a TG level above 400 mg/dl. The cited portions of Hayashi further do not disclose or
2 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
3 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
4 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
5 high TG levels.

6 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
7 claims), Hayashi does not disclose or suggest a subject with the recited very high TG levels who
8 does not receive concurrent lipid altering therapy. Hayashi also does not disclose or suggest the
9 claimed pharmaceutical composition with the recited fatty acids compositions or administration
10 period. With respect to Claim 13, Hayashi further does not disclose or suggest a method to
11 effect a statistically significant reduction in TG without effecting a statistically significant
12 increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1
13 and 17, Hayashi further does not disclose or suggest a method of reducing triglycerides and
14 apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about
15 1500 mg/dl.

16 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
17 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
18 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
19 Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant
20 reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the
21 subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to
22 disclose or suggest the subject and second subject consume a Western diet. With respect to
23 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
24

1 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
2 comparison to the second subject.

3 (6) Katayama

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

8 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
9 Katayama disclose or suggest elements of the '715 Claims. The cited portions of Katayama do
10 not disclose or suggest these elements at least because they do not disclose or suggest
11 administration of EPA with the recited purity to a subject with the recited very high TG levels
12 who does not receive concurrent lipid altering therapy. The cited portions of Katayama further
13 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
14 compositions or dosage. The cited portions of Katayama further do not disclose or suggest a
15 method to effect a statistically significant reduction in TG without effecting a statistically
16 significant increase in LDL-C or Apo-B in the subject.

17 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
18 claims), Katayama does not disclose or suggest a subject with the recited very high TG levels
19 who does not receive concurrent lipid altering therapy. Katayama also does not disclose or
20 suggest the claimed pharmaceutical composition with the recited fatty acid compositions dosage.

21 With respect to Claim 13, Katayama further does not disclose or suggest a method to effect a
22 statistically significant reduction in TG without effecting a statistically significant increase in
23 LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Katayama further does not
24

1 disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a
2 fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

3 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
4 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
5 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
6 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
7 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
8 comparison to the second subject. With respect to Claim 14, this reference fails to disclose or
9 suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting
10 a statistically significant increase in LDL-C in the subject. With respect to Claims 11, 15, and
11 18, this reference fails to disclose or suggest the subject and second subject consume a Western
12 diet.

13 (7) Leigh-Firbank

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

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
18 Leigh-Firbank disclose or suggest elements of the '715 Claims. The cited portions of Leigh-
19 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
20 administration of EPA with the recited purity to a subject with the recited very high TG levels
21 who does not receive concurrent lipid altering therapy. The cited portions of Leigh-Firbank
22 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty
23 acid compositions, dosage, or administration period. The cited portions of Leigh-Firbank further
24 do not disclose or suggest a method of administering the claimed pharmaceutical composition to

1 effect a statistically significant reduction in TG without effecting a statistically significant
2 increase in LDL-C or Apo-B in the subject.

3 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
4 claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG
5 levels who does not receive concurrent lipid altering therapy. Leigh-Firbank also does not
6 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
7 compositions, dosage, or administration period. With respect to Claim 13, Leigh-Firbank further
8 does not disclose or suggest a method of administering the claimed pharmaceutical composition
9 to effect a statistically significant reduction in TG without effecting a statistically significant
10 increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Leigh-Firbank
11 further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a
12 subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

13 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
14 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
15 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
16 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
17 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
18 comparison to the second subject. Further, with respect to Claim 14, this reference fails to
19 disclose or suggest the administration of the claimed pharmaceutical composition to effect a
20 statistically significant reduction in TG and Apo-B without effecting a statistically significant
21 increase in LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to
22 disclose or suggest the subject and second subject consume a Western diet.

23 (8) Lovaza PDR

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

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
2 Lovaza PDR disclose or suggest elements of the '715 Claims. The cited portions of the Lovaza
3 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
4 administration of EPA with the recited purity to a subject with the recited very high TG levels.
5 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed
6 pharmaceutical composition with the recited fatty acid compositions or administration period.
7 The cited portions of the Lovaza PDR further do not disclose or suggest a method of
8 administering the claimed pharmaceutical composition to effect a statistically significant
9 reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B.

10 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
11 claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition
12 with the recited fatty acid compositions or administration period. With respect to Claim 13, the
13 Lovaza PDR further does not disclose or suggest a method of administering the claimed
14 pharmaceutical composition to effect a statistically significant reduction in TG without effecting
15 a statistically significant increase in LDL-C or Apo-B. With respect to Claims 1 and 17, the
16 Lovaza PDR further does not disclose or suggest a method of reducing apolipoprotein B.

17 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
18 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels. With
19 respect to Claim 14, this reference fails to disclose or suggest the administration of the claimed
20 pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B
21 without effecting a statistically significant increase in LDL-C. With respect to Claims 11, 15,
22 and 18, this reference fails to disclose or suggest the subject and second subject consume a
23 Western diet.

24
CONFIDENTIAL

1 (9) Maki

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

4 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
5 disclose or suggest elements of the '715 Claims. The cited portions of Maki do not disclose or
6 suggest these elements at least because they do not disclose or suggest administration of EPA
7 with the recited purity to a subject with the recited very high TG levels who does not receive
8 concurrent lipid altering therapy. The cited portions of Maki further do not disclose or suggest
9 the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
10 administration period. The cited portions of Maki further do not disclose or suggest a method of
11 administering the claimed pharmaceutical composition to effect a statistically significant
12 reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the
13 subject.

14 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
15 claims), Maki does not disclose or suggest a subject with the recited very high TG levels who
16 does not receive concurrent lipid altering therapy. Maki also does not disclose or suggest the
17 claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or
18 administration period. With respect to Claim 13, Maki further does not disclose or suggest a
19 method of administering the claimed pharmaceutical composition to effect a statistically
20 significant reduction in TG without effecting a statistically significant increase in LDL-C or
21 Apo-B in the subject. With respect to Claims 1 and 17, Maki further does not disclose or suggest
22 a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline
23 triglyceride level of 500 mg/dl to about 1500 mg/dl.

1 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
2 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
3 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
4 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
5 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
6 comparison to the second subject. With respect to Claim 14, this reference fails to disclose or
7 suggest the administration of the claimed pharmaceutical composition to effect a statistically
8 significant reduction in TG and Apo-B without effecting a statistically significant increase in
9 LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to disclose or
10 suggest the subject and second subject consume a Western diet.

11 (10) Matsuzawa

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

14 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
15 Matsuzawa disclose or suggest elements of the '715 Claims. The cited portions of Matsuzawa
16 do not disclose or suggest these elements at least because they do not disclose or suggest
17 administration of EPA with the recited purity to a subject with the recited very high TG levels
18 who does not receive concurrent lipid altering therapy. The cited portions of Matsuzawa further
19 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
20 compositions or dosage. The cited portions of Matsuzawa further do not disclose or suggest a
21 method of administering the claimed pharmaceutical composition to effect a statistically
22 significant reduction in TG without effecting a statistically significant increase in LDL-C or
23 Apo-B in the subject.

24

1 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
2 claims), Matsuzawa does not disclose or suggest a subject with the recited very high TG levels
3 who does not receive concurrent lipid altering therapy. Matsuzawa also does not disclose or
4 suggest the claimed pharmaceutical composition with the recited fatty acid compositions dosage.
5 With respect to Claim 13, Matsuzawa further does not disclose or suggest a method of
6 administering the claimed pharmaceutical composition to effect a statistically significant
7 reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the
8 subject. With respect to Claims 1 and 17, Matsuzawa further does not disclose or suggest a
9 method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline
10 triglyceride level of 500 mg/dl to about 1500 mg/dl.

11 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
12 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
13 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
14 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
15 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
16 comparison to the second subject. With respect to Claim 14, this reference fails to disclose or
17 suggest a method the administration of the claimed pharmaceutical composition to effect a
18 statistically significant reduction in TG and Apo-B without effecting a statistically significant
19 increase in LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to
20 disclose or suggest the subject and second subject consume a Western diet.

21 (11) Mori 2000

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

24
CONFIDENTIAL

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
2 2000 disclose or suggest elements of the '715 Claims. The cited portions of Mori 2000 do not
3 disclose or suggest these elements at least because they do not disclose or suggest administration
4 of EPA with the recited purity to a subject with the recited very high TG levels who does not
5 receive concurrent lipid altering therapy. The cited portions of Mori 2000 further do not disclose
6 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
7 administration period. The cited portions of Mori 2000 further do not disclose or suggest a
8 method to effect a statistically significant reduction in TG without effecting a statistically
9 significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

10 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
11 claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG levels
12 who does not receive concurrent lipid altering therapy. Mori 2000 also does not disclose or
13 suggest the claimed pharmaceutical composition with the recited fatty acids compositions or
14 administration period. With respect to Claim 13, Mori 2000 further does not disclose or suggest
15 a method to effect a statistically significant reduction in TG without effecting a statistically
16 significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect
17 to Claims 1 and 17, Mori 2000 further does not disclose or suggest a method of reducing
18 triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500
19 mg/dl to about 1500 mg/dl.

20 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
21 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
22 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
23 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
24

1 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
2 comparison to the second subject. With respect to Claim 14, this reference fails to disclose or
3 suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting
4 a statistically significant increase in LDL-C in the subject with the claimed TG level. With
5 respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second
6 subject consume a Western diet.

7 (12) Mori 2006

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

10 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
11 2006 disclose or suggest elements of the '715 Claims. The cited portions of Mori 2006 do not
12 disclose or suggest these elements at least because they do not disclose or suggest administration
13 of EPA with the recited purity to a subject with the recited very high TG levels who does not
14 receive concurrent lipid altering therapy. The cited portions of Mori 2006 further do not disclose
15 or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited
16 portions of Mori 2006 further do not disclose or suggest a method to effect a statistically
17 significant reduction in TG without effecting a statistically significant increase in LDL-C or
18 Apo-B in the subject.

19 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
20 claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG levels
21 who does not receive concurrent lipid altering therapy. Mori 2006 also does not disclose or
22 suggest the claimed pharmaceutical composition with the recited fatty acid dosage. With respect
23 to Claim 13, Mori 2006 further does not disclose or suggest a method to effect a statistically
24 significant reduction in TG without effecting a statistically significant increase in LDL-C or

1 Apo-B in the subject. With respect to Claims 1 and 17, Mori 2006 further does not disclose or
2 suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting
3 baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

4 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
5 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
6 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
7 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
8 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
9 comparison to the second subject. Further, with respect to Claim 14, this reference fails to
10 disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B
11 without effecting a statistically significant increase in LDL-C in the subject with the claimed TG
12 level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the
13 subject and second subject consume a Western diet.

14 (13) Nozaki

15 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
16 purity of the composition is reported as 90%. The study was not placebo controlled and was
17 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
18 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
19 patient population.

20 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
21 ‘715 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
22 administration of EPA with the recited purity to a subject with the recited very high TG levels
23 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
24 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

1 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
2 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
3 with the recited very high TG levels.

4 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
5 '715 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
6 because they do not disclose or suggest administration of EPA with the recited purity to a subject
7 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
8 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
9 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
10 further do not disclose or suggest a method to effect the recited TG reduction without
11 substantially increasing LDL-C.

12 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
13 claims), Nozaki does not disclose or suggest a subject with the recited very high TG levels who
14 does not receive concurrent lipid altering therapy. Nozaki also does not disclose or suggest the
15 claimed pharmaceutical composition with the recited fatty acids compositions or administration
16 period. With respect to Claim 13, Nozaki further does not disclose or suggest a method to effect
17 a statistically significant reduction in TG without effecting a statistically significant increase in
18 LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17,
19 Nozaki further does not disclose or suggest a method of reducing triglycerides and
20 apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about
21 1500 mg/dl.

22 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
23 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
24

1 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
2 Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant
3 reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the
4 subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to
5 disclose or suggest the subject and second subject consume a Western diet. With respect to
6 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
7 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
8 comparison to the second subject.

9 (14) Omacor PDR

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

11 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
12 Omacor PDR disclose or suggest elements of the '715 Claims. The cited portions of the Omacor
13 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
14 administration of EPA with the recited purity to a subject with the recited very high TG levels.
15 The cited portions of the Omacor PDR further do not disclose or suggest the claimed
16 pharmaceutical composition with the recited fatty acid compositions or administration period.
17 The cited portions of the Omacor PDR further do not disclose or suggest a method of
18 administering the claimed pharmaceutical composition to effect a statistically significant
19 reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B.

20 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
21 claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition
22 with the recited fatty acid compositions or administration period. With respect to Claim 13, the
23 Omacor PDR further does not disclose or suggest a method of administering the claimed
24 pharmaceutical composition to effect a statistically significant reduction in TG without effecting

1 a statistically significant increase in LDL-C or Apo-B. With respect to Claims 1 and 17, the
2 Omacor PDR further does not disclose or suggest a method of reducing triglycerides and
3 apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about
4 1500 mg/dl.

5 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
6 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
7 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
8 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
9 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
10 comparison to the second subject. Further, with respect to Claim 14, this reference fails to
11 disclose or suggest the administration of the claimed pharmaceutical composition to effect a
12 statistically significant reduction in TG and Apo-B without effecting a statistically significant
13 increase in LDL-C. With respect to Claims 11, 15, and 18, this reference fails to disclose or
14 suggest the subject and second subject consume a Western diet.

15 (15) Satoh

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

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
20 Satoh disclose or suggest elements of the ‘715 Claims. The cited portions of Satoh do not
21 disclose or suggest these elements at least because they do not disclose or suggest administration
22 of EPA with the recited purity to a subject with the recited very high TG levels who does not
23 receive concurrent lipid altering therapy. The cited portions of Satoh further do not disclose or
24 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or

1 dosage. The cited portions of Satoh further do not disclose or suggest a method to effect a
2 statistically significant reduction in TG without effecting a statistically significant increase in
3 LDL-C or Apo-B in the subject with the claimed TG level.

4 With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted
5 claims), Satoh does not disclose or suggest a subject with the recited very high TG levels who
6 does not receive concurrent lipid altering therapy. Satoh also does not disclose or suggest the
7 claimed pharmaceutical composition with the recited fatty acids compositions or dosage. With
8 respect to Claim 13, Satoh further does not disclose or suggest a method to effect a statistically
9 significant reduction in TG without effecting a statistically significant increase in LDL-C or
10 Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Satoh further
11 does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject
12 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

13 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
14 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
15 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
16 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
17 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
18 comparison to the second subject. Further, with respect to Claim 14, this reference fails to
19 disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B
20 without effecting a statistically significant increase in LDL-C in the subject with the claimed TG
21 level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the
22 subject and second subject consume a Western diet.

1 (16) Shinozaki

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

4 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
5 Shinozaki disclose or suggest elements of the '715 Claims. The cited portions of Shinozaki do
6 not disclose or suggest these elements at least because they do not disclose or suggest
7 administration of EPA with the recited purity to a subject with the recited very high TG levels
8 who does not receive concurrent lipid altering therapy. The cited portions of Shinozaki further
9 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
10 compositions or dosage. The cited portions of Shinozaki further do not disclose or suggest a
11 method to effect a statistically significant reduction in TG without effecting a statistically
12 significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

13 With respect to Claim 1, 13, and 17 of the '715 Patent (and therefore all asserted claims),
14 Shinozaki does not disclose or suggest a subject with the recited very high TG levels who does
15 not receive concurrent lipid altering therapy. Shinozaki also does not disclose or suggest the
16 claimed pharmaceutical composition with the recited fatty acids compositions or dosage. With
17 respect to Claim 13, Shinozaki further does not disclose or suggest a method to effect a
18 statistically significant reduction in TG without effecting a statistically significant increase in
19 LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17,
20 Shinozaki further does not disclose or suggest a method of reducing triglycerides and
21 apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about
22 1500 mg/dl.

23 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
24 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject

1 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
2 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
3 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
4 comparison to the second subject. Further, with respect to Claim 14, this reference fails to
5 disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B
6 without effecting a statistically significant increase in LDL-C in the subject with the claimed TG
7 level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the
8 subject and second subject consume a Western diet.

9 (17) Takaku

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

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Takaku disclose or suggest elements of the ‘715 Claims. The cited portions of Takaku do not
14 disclose or suggest these elements at least because they do not disclose or suggest administration
15 of EPA with the recited purity to a subject with the recited very high TG levels who does not
16 receive concurrent lipid altering therapy. The cited portions of Takaku further do not disclose or
17 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
18 dosage. The cited portions of Takaku further do not disclose or suggest a method of
19 administering the claimed pharmaceutical composition to effect a statistically significant
20 reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the
21 subject.

22 With respect to Claims 1, 13, and 17 of the ‘715 Patent (and therefore all asserted
23 claims), Takaku does not disclose or suggest a subject with the recited very high TG levels who
24 does not receive concurrent lipid altering therapy. Takaku also does not disclose or suggest the

1 claimed pharmaceutical composition with the recited fatty acid compositions dosage. With
2 respect to Claim 13, Takaku further does not disclose or suggest a method of administering the
3 claimed pharmaceutical composition to effect a statistically significant reduction in TG without
4 effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to
5 Claims 1 and 17, Takaku further does not disclose or suggest a method of reducing triglycerides
6 and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to
7 about 1500 mg/dl.

8 Further, with respect to Claim 4, this reference fails to disclose or suggest a method to
9 effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject
10 having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to
11 Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,
12 VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a
13 comparison to the second subject. Further, with respect to Claim 14, this reference fails to
14 disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B
15 without effecting a statistically significant increase in LDL-C in the subject with the claimed TG
16 level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the
17 subject and second subject consume a Western diet.

18 c) The Prior Art Does Not Render the Claims Obvious

19 Defendants have not identified by clear and convincing evidence that the asserted claims
20 of the '715 Patent would have been *prima facie* obvious in light of the references cited, either
21 alone or in combination. As described above, none of the references discloses all of the elements
22 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
23 explanation, and argue they somehow must be combined to render obvious the asserted claims.
24 Where Defendants have failed to make disclosures with the specificity required by Local Patent

1 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
2 claim elements at issue.

3 Defendants' contentions fail to disclose each and every element of the claims of the '715
4 patent. Specifically, Defendants do not contend that the relied upon references disclose the
5 following elements of Claims 1-19: (1) a subject having a fasting baseline triglyceride level of
6 500 mg/dl to about 1500 mg/dl *who does not receive concurrent lipid altering therapy*; or (2)
7 administering the claimed pharmaceutical composition to the recited subject to effect a
8 statistically significant reduction in triglycerides without effecting a statistically significant
9 increase in LDL-C or Apolipoprotein B in the subject. Therefore, Defendants' prior art
10 combinations cannot render the claims *prima facie* obvious.

11 Facts supporting the non-obviousness of the claims of the '715 patent are discussed in
12 detail below. The objective indicia discussed in Section V.O further demonstrate that the '715
13 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims
14 would have been obvious.

- 15 (1) Defendants Do Not Demonstrate that the Independent
16 Claims of the '715 Patent Would Have Been Obvious
- 17 (a) Defendants Do Not Demonstrate that a Person of
18 Ordinary Skill in the Art Would Have Had Any
Reason to Replace the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA
- 19 (i) The '715 Patent is not Obvious Over the
20 Omacor PDR/Lovaza PDR in combination
with the known clinical benefits of
21 administering pure EPA as evidenced by
Katayama and/or Matsuzawa, further in
22 view of Nozaki and/or Hayashi, and further
in view of Leigh-Firbank and/or Mori 2000

23
24
CONFIDENTIAL

(and/or Satoh or Shinozaki in view of Contacos)

With respect to the '715 Patent, Defendants present a combination of ten references:

“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 (and/or Satoh or Shinozaki in view of Contacos).”¹⁰⁸⁹ 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.^{1090, 1091} 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.¹⁰⁹² Defendants’ unsupported cobbling of selective disclosures

¹⁰⁸⁹ Defendants’ Joint Invalidation Contentions at 255.

¹⁰⁹⁰ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as described in the references cited above in section V.B.2) in view of, at least, the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidation Contentions at 254.

¹⁰⁹¹ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C.,” and that “[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidation Contentions at 253.

¹⁰⁹² *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*

1 represents hindsight reconstruction.¹⁰⁹³ Defendants’ contentions are no more than an assertion
2 that certain claim elements were known in the prior art. Throughout their contentions,
3 Defendants’ selectively cite to data points in a reference without considering other disclosures or
4 even the reference as a whole. Each reference, however, must be evaluated for all that it
5 teaches.¹⁰⁹⁴ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

7 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
8 triglycerides in a subject with the claimed pharmaceutical composition containing the claimed
9 fatty acid compositions or administration period. The Lovaza PDR further does not disclose a
10 method to effect the specified TG reduction without substantially increasing LDL-C or Apo-B.
11 Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza
12 causes a significant increase in LDL-C levels in the very high TG patient population, for whom
13 the product is indicated. The Lovaza PDR does not disclose any Apo-B effects when Lovaza
14 was administered to the very high TG patient population. At most, the Lovaza PDR discloses
15 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375

17
18 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 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).

¹⁰⁹³ 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”).

¹⁰⁹⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500
2 mg/dL) TG levels.

3 The proposed combinations do not render the independent claims of the '715 Patent
4 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
5 considered Matsuzawa, Katayama, Mori 2000, Satoh, Shinozaki Contacos, and Lovaza (both
6 generally and the Lovaza package insert specifically) during prosecution.¹⁰⁹⁵

7 The analysis of the independent claims of the '715 Patent are incorporated into all
8 asserted claims that depend from this Claim.

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

12 For an invention to be obvious, there must have been an "apparent reason" to make it.
13 The subject matter of the '715 patent claims would not have been obvious in light of these
14 references because a person of ordinary skill would not have been motivated to purify EPA or
15 been able to reasonably expect that the claimed pharmaceutical composition would effect a
16 statistically significant reduction in TG levels without effecting a statistically significant
17 increase in LDL-C or Apo-B levels.

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

20 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
21 safety and efficacy of Epedel in patients with a wide range of baseline TG levels. These studies

22 _____
23 ¹⁰⁹⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
2 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
3 art would not and could not attribute any observed effect (and the magnitude of that effect) to
4 that of the drug. Any observed effect could be placebo dependent.¹⁰⁹⁶ As discussed above in
5 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
6 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG
7 patients because patients with higher TG levels had different lipid responses compared to
8 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
9 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
10 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary
11 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
12 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
13 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
14 high or high TG patients, was expected. At the priority date of the '715 patent, a person of
15 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
16 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
17 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
18 lowering through increased VLDL particle conversion.

19 Defendants argue that these studies disclose known “clinical benefits” of administering
20 pure EPA, lowering triglycerides without raising LDL-C.¹⁰⁹⁷ This is an incorrect characterization
21

22 ¹⁰⁹⁶See Grimsgaard at 652 (Although administration of EPA reduced Apo-B compared to baseline, it was not a
23 statistically significant effect when compared to placebo. Grimsgaard’s disclosure highlights the importance of a
24 placebo-controlled study and why results compared only to baseline may be misleading.)

¹⁰⁹⁷ Defendants’ Joint Invalidity Contentions at 255.

1 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
2 long term treatment of Epedel and its ability to lower both serum total cholesterol and TG levels.
3 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
4 Defendants’ selective citation of LDL-C data from these references represents the improper use
5 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
6 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
7 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
8 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
9 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.¹⁰⁹⁸ The
10 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
11 would a person of ordinary skill view these references as teaching such a benefit for very-high
12 TG patients.

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

17 In addition, Katayama and Matsuzawa do not disclose the purity of the Epedel used. The
18 purity of Epedel has varied over time and across different formulations of the product, therefore
19 it is difficult to determine the purity of the version of Epedel used unless it is specified by the
20 disclosure. One cannot simply rely on the fact that Epedel was administered and assume that the
21 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
22 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
23

24 ¹⁰⁹⁸ Defendants’ Joint Invalidity Contentions at 255.

1 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.
2 Nishikawa,¹⁰⁹⁹ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
3 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
4 purity.¹¹⁰⁰

5 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
6 patients. These studies would not have been extrapolated to Western populations because the
7 Japanese diet contains much more fish and has a number of other different attributes. The
8 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
9 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
10 the patient population is exclusively Japanese cannot be generalized to other populations.¹¹⁰¹
11 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
12 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
13 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
14 that the Japanese respond differently to lipid lowering agents than Westerners.

15 Defendants rely on Katayama to demonstrate the "known clinical benefits of
16 administering pure EPA - lowering triglycerides without raising LDL-C."¹¹⁰² However,
17 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
18 treatment in patients with hyperlipidemia.¹¹⁰³ Katayama does not disclose *any* LDL-C related

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20 ¹⁰⁹⁹ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

21 ¹¹⁰⁰ See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

22 ¹¹⁰¹ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

23 ¹¹⁰² Defendants' Joint Invalidity Contentions at 255.

24 ¹¹⁰³ Katayama at 2.

1 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
2 reference to provide any such disclosure. The only results disclosed by Katayama were a
3 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
4 administered to patients with borderline-high to high TG levels, and its safety for long term use
5 in this patient population.¹¹⁰⁴ In addition to Katayama’s lack of disclosure regarding LDL-C,
6 Defendants identify no other basis upon which a person of ordinary skill would have sought to
7 combine the composition disclosed in Katayama with the Lovaza PDR.

8 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
9 administering pure EPA - lowering triglycerides without raising LDL-C.”¹¹⁰⁵ However,
10 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
11 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
12 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
13 were evaluated for improvement in serum triglycerides levels.¹¹⁰⁶ It is unclear which of the 26
14 patients were included in each separate evaluation; therefore one cannot determine the baseline
15 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
16 of a placebo control makes it less likely that the results of this study can be generalized as an
17 effect on any population as a whole and provides no insight with respect to the very-high TG
18 patient population.

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22 ¹¹⁰⁴ *Id.* at 16.

23 ¹¹⁰⁵ Defendants’ Joint Invalidation Contentions at 255.

24 ¹¹⁰⁶ Matsuzawa at 7 and 19.

1 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
2 and one participant with TG levels > 1,000 mg/dL.¹¹⁰⁷ However, when analyzing the lipid
3 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
4 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
5 triglyceride levels.”¹¹⁰⁸ Fig. 4, which depicts the changes in serum triglycerides, shows that the
6 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
7 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
8 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
9 undisclosed purity). The identification of three patients with TG levels between 400 and less
10 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of
11 ordinary skill would not understand that the reference makes any such disclosure. As discussed
12 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
13 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
14 evidence to the contrary.

15 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
16 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.¹¹⁰⁹ The disclosure
17 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
18 excluded from the LDL-C results because the Friedewald’s Equation was used to calculate LDL-
19 C levels. The Friedewald’s Equation cannot be used for patients with triglyceride levels of at
20 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

22 ¹¹⁰⁷ *Id.* at 23.

23 ¹¹⁰⁸ *Id.* at 10.

24 ¹¹⁰⁹ *Id.* at 11.

1 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
2 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
3 skill in the art, however, would have expected the same treatment in patients with very high TG
4 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
5 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
6 triglyceride levels.¹¹¹⁰ At best, Matsuzawa demonstrates the uncertainty and confusion related to
7 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
8 any other basis upon which a person of ordinary skill would have sought to combine the
9 composition disclosed in Matsuzawa with the Lovaza PDR.

10 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
11 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
12 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
13 increases LDL-C.¹¹¹¹ Defendants identify no other basis upon which a person of ordinary skill
14 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
15 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
16 asserted claims of the '715 patent.

17 (ii) Nozaki or Hayashi Do Not
18 Disclose Purported Known
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22 ¹¹¹⁰ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
23 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
24 compositions used, or identify the patient populations were observed.

¹¹¹¹ *See, e.g.,* Rambjor.

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3 Defendants contend that Nozaki and Hayashi disclose the purported known clinical
4 benefit of administering pure EPA, lowering TGs “without raising Apolipoprotein B.”¹¹¹²
5 Nozaki and Hayashi do not disclose or suggest “a statistically significant reduction in
6 triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B”
7 when purified EPA is administered to the very high TG patient population as the claims of the
8 ‘715 Patent require.

9 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
10 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
11 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
12 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
13 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
14 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
15 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
16 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
17 patient population were abnormally high and would not have relied upon these results. Further,
18 the person of skill in the art would not have looked to this patient population to predict the Apo-
19 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
20 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
21 levels.¹¹¹³ Nozaki does not provide a motivation or reasonable expectation of success for
22 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and

23 ¹¹¹² Defendants’ Joint Invalidity Contentions at 255-256.

24 ¹¹¹³ Nozaki at 256.

1 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
2 effect “a statistically significant reduction in triglycerides without effecting a statistically
3 significant increase in LDL-C or Apolipoprotein B in the subject” as the claims of the ‘715
4 Patent require.

5 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
6 the EPA and the DHA content in the composition that was administered is unknown. A person
7 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
8 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
9 C were not statistically significant.¹¹¹⁴ Further, the person of skill in the art would not have
10 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
11 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
12 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
13 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
14 to effect “a statistically significant reduction in triglycerides without effecting a statistically
15 significant increase in LDL-C or Apolipoprotein B in the subject” as the claims of the ‘715
16 Patent require.

17 Further, Hayashi was a small study conducted in only Japanese patients and was not
18 placebo controlled. This study would not have been extrapolated to Western populations
19 because the Japanese diet contains much more fish and has a number of other different attributes.
20 The Japanese consume a higher amount of EPA and DHA in their diets than Western
21 populations. In fact, Defendants’ own reference states that the results from studies where the
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23 ¹¹¹⁴ Hayashi at 26, Table I.
24

1 patient population is exclusively Japanese cannot be generalized to other populations.¹¹¹⁵ The
2 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
3 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
4 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
5 the Japanese respond differently to lipid lowering agents than Westerners.

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

11 (iii) Leigh-Firbank and/or Mori
12 2000 (and/or Satoh or
13 Shinozaki in view of
14 Contacos) Do Not Disclose
Purported Knowledge that
DHA was Responsible for the
Increase in LDL-C

15 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
16 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
17 C levels.”¹¹¹⁶ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
18 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
19 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
20 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
21 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As

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23 ¹¹¹⁵ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
other populations.”).

24 ¹¹¹⁶ Defendants’ Joint Invalidity Contentions at 258.

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

10 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
11 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
12 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
13 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
14 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
15 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
16 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
17 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
18 acknowledges that EPA- and DHA-enriched oils, which contained other saturated and
19 polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and
20 DHA.¹¹¹⁷ A person of ordinary skill would understand that studies directed to EPA and DHA-
21 enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid
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24 ¹¹¹⁷ Mori 2006 at 96.

1 parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
2 Firbank, because purified EPA and DHA were not administered separately.

3 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
4 effects of EPA and DHA individually, even though it administered a combination of EPA and
5 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
6 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
7 phospholipid EPA were *independently* associated with the decrease in fasting TGs,¹¹¹⁸ and DHA
8 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
9 of the art and numerous publications cited by Defendants.¹¹¹⁹ It is widely accepted that DHA
10 also has a hypotriglyceridemic effect.

11 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
12 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
13 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
14 away from the claimed invention. “A reference may be said to teach away when a person of
15 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
16 out in the reference, or would be led in a direction divergent from the path that was taken by the
17 applicant.”¹¹²⁰ Although teaching away is fact-dependent, “in general, a reference will teach

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22 ¹¹¹⁸ Leigh-Firbank at 440.

23 ¹¹¹⁹ See, e.g. Grimsgaard at 654.

24 ¹¹²⁰ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

1 away if it suggests that the line of development flowing from the reference’s disclosures is
2 unlikely to be productive of the result sought by the applicant.”¹¹²¹

3 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
4 a more favorable lipid profile than after EPA supplementation.”¹¹²² For example, it states that
5 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
6 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
7 effects on fasting glucose concentrations.”¹¹²³ Mori 2000 also states that “[d]espite an increase
8 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
9 be favorable.”¹¹²⁴ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
10 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
11 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
12 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
13 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
14 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
15 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
16 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
17 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
18 would have sought to combine Mori 2000 with the Lovaza PDR.

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21 ¹¹²¹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
(Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
(“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

22 ¹¹²² Mori 2000 at 1092.

23 ¹¹²³ Mori 2000 at 1088.

24 ¹¹²⁴ Mori 2000 at 1092.

1 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
2 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
3 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
4 has little effect on LDL-C levels.¹¹²⁵ Defendants identify no other basis upon which a person of
5 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
6 Leigh-Firbank and/or Mori 2000.

7 Defendants purport to formulate an obviousness argument that relies on Satoh or
8 Shinozaki in view of Contacos.^{1126,1127} However, Defendants fail to provide any factual or legal
9 basis as to why Satoh, Shinozaki, or Contacos disclose a claim element, an “apparent reason” or
10 motivation to combine the elements in the manner claimed,¹¹²⁸ or “a reasonable expectation of
11 success”¹¹²⁹ of achieving the claimed invention.

12 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
13 pravastatin, but it does not disclose administration of EPA of the recited composition. Contacos
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15 ¹¹²⁵ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

16 ¹¹²⁶ Defendants’ Joint Invalidity Contentions at 255.

17 ¹¹²⁷ Further, it is not apparent what combination or combinations of references Defendants assert in their purported
18 obviousness argument based on “Lovaza PDR in combination with . . . Katayama and/or Matsuzawa, and further in
19 view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos).” In failing to identify the
20 role of “Satoh or Shinozaki in view of Contacos” in this purported obviousness combination or offer any associated
21 explanation, they have failed to meet their contentions burden. Accordingly, defendants should be precluded from
22 relying on this purported combination.

23 ¹¹²⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
24 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

¹¹²⁹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 demonstrated that fish oil does not increase LDL-C or Apo-B when administered to patients.
2 Contacos also fails to provide motivation to administer purified EPA to a very high TG patient
3 population and does not provide any reasonable expectation of success in lowering TG levels in
4 the very high TG patient population without increasing LDL-C or Apo-B.

5 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
6 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
7 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
8 compared to baseline, there was no significant effect when compared to placebo.¹¹³⁰ Satoh does
9 not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a
10 person of ordinary skill view these references as teaching such a benefit for very-high TG
11 patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to
12 increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary.
13 A person of ordinary skill in the art, however, would have expected that fish oils (and other TG
14 lowering agents) would substantially increase LDL-C in patients with very high TG levels. In
15 addition, Satoh does not disclose the effect of EPA on Apo-B. Satoh fails to provide motivation
16 to administer purified EPA to a very high TG patient population and does not provide any
17 reasonable expectation of success in lowering TG levels in the very high TG patient population
18 without increasing LDL-C or Apo-B.

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

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24 ¹¹³⁰ Satoh at 145.

1 states that the results from studies where the patient population is exclusively Japanese cannot be
2 generalized to other populations.¹¹³¹ The Japanese diet comprises between 8 and 15 times more
3 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
4 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
5 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
6 agents than Westerners.

7 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a))
8 and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.
9 Shinozaki says nothing about an LDL-C or Apo-B effect because it measured only LDL particle
10 number and Lp(a), and did not measure LDL-C or Apo-B. The finding disclosed by Shinozaki
11 was that “long term administration of EPA may lower Lp(a) and serum lipids.”¹¹³² In addition to
12 Shinozaki’s lack of disclosure regarding LDL-C or Apo-B, Defendants identify no other basis
13 upon which a person of ordinary skill would have sought to combine the composition disclosed
14 in Shinozaki.

15 Defendants identify no other basis upon which a person of ordinary skill would have
16 sought to combine the “Lovaza PDR in combination with . . . Katayama and/or Matsuzawa, and
17 further in view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of
18 Contacos).”

- 19 (ii) The ‘715 Patent is not Obvious Over the
20 Omacor PDR/Lovaza PDR, in Combination
21 with Katayama and/or Matsuzawa, and/or
22 Takaku, Further in View of Nozaki and/or

23 ¹¹³¹ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
other populations.”).

24 ¹¹³² Shinozaki at 107-109.

With respect to the '715 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.”¹¹³³

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.¹¹³⁴ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.¹¹³⁵ Defendants’ contentions are no more than an assertion that certain

¹¹³³ Defendants’ Joint Invalidity Contentions at 255-56.

¹¹³⁴ 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).

¹¹³⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 claim elements were known in the prior art. Throughout their contentions, Defendants’
2 selectively cite to data points in a reference without considering other disclosures or even the
3 reference as a whole. Each reference, however, must be evaluated for all that it teaches.¹¹³⁶
4 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

5 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
6 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
7 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
8 further do not disclose a method to effect the claimed TG reduction without substantially
9 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
10 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
11 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
12 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
13 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
14 mg/dL) TG levels. The proposed combinations do not render the independent claims of the ’715
15 Patent obvious and Defendants’ burden to prove otherwise is especially difficult because the
16 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
17 generally and the Lovaza package insert specifically) during prosecution.¹¹³⁷

18 The analysis of the independent claims of the ’715 Patent is incorporated into all asserted
19 claims that depend from this Claim.

20 (a) A Person of Ordinary Skill Would
21 Not Have Been Motivated to

22 ¹¹³⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹¹³⁷ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

3 For an invention to be obvious, there must have been an “apparent reason” to make it.
4 The subject matter of the ‘715 patent claims would not have been obvious in light of these
5 references because a person of ordinary skill would not have been motivated to purify EPA or
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
7 levels without an increase in LDL-C levels.

8 (i) Grimsgaard, Katayama,
9 Matsuzawa and/or Takaku
10 Do Not Disclose Purported
Known Clinical Benefits of
Administering Pure EPA

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

18 Defendants also rely on Grimsgaard to support their assertion that “administration of
19 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”¹¹³⁸ However,
20 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
21 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

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¹¹³⁸ Defendants’ Joint Invalidity Contentions at 259.

1 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
2 administered to people with normal triglyceride levels for 7 weeks.¹¹³⁹ The results from the
3 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
4 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
5 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
6 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
7 better maintained with oil rich in DHA than oil rich in EPA.”¹¹⁴⁰ Although Grimsgaard states
8 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
9 comment on EPA’s effect on LDL-C.

10 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
11 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
12 LDL-C by EPA, as confirmation “that administration of purified DHA results in increased LDL-
13 C levels while administration of purified EPA resulted in a decrease in LDL-C levels.”¹¹⁴¹ The
14 results of Grimsgaard, reproduced below, show that EPA and DHA’s impact on LDL-C were the
15 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo’s
16 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to
17 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard’s
18 disclosure highlights the importance of a placebo-controlled study and why results compared
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22 ¹¹³⁹ Defendants state in their Joint Invalidation Contentions at 211 that Grimsgaard was conducted in patients with TG
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

¹¹⁴⁰ Grimsgaard at 654.

¹¹⁴¹ Defendants’ Joint Invalidation Contentions at 259 n.33.

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)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	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 ²	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 ²	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 ²	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ²	0.96 ± 0.13	0.04 ± 0.08 ²	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 ²	4.70 ± 1.24	-0.13 ± 0.47 ²	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 $\bar{x} \pm$ SD.

²⁻⁵ 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.”¹¹⁴² 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.”¹¹⁴³ 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

¹¹⁴² Grimsgaard at 657.

¹¹⁴³ Grimsgaard at 654.

1 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
2 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
3 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
4 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
5 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
6 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
7 not have statistically significantly effects on LDL-C compared to placebo.¹¹⁴⁴ A person of
8 ordinary skill would not draw conclusions regarding differences between EPA and DHA based
9 on statistically insignificant results.

10 Defendants also rely on Takaku to support their assertion that “clinical benefits of
11 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
12 art.¹¹⁴⁵ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
13 safety of Epadel (of undisclosed purity)¹¹⁴⁶ based on long-term administration.¹¹⁴⁷

14 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
15 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
16 acknowledges that “only a few subjects were examined” and cautions against drawing a
17

18 ¹¹⁴⁴In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
19 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
20 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
21 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
22 such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
23 no impact on LDL-C levels.

21 ¹¹⁴⁵ Defendants’ Joint Invalidity Contentions at 256.

22 ¹¹⁴⁶ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
23 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
24 Nakamura at 23 (Epadel with purity > 90%).

¹¹⁴⁷ Takaku at ICOSAPENT_DFNDT00006834.

1 conclusion “only from the results of the present study.”¹¹⁴⁸ Because the study did not include
2 any placebo control, a person of ordinary skill in the art would understand these reports do not
3 provide the ability to conclude that the observed lipid effects would have occurred independent
4 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
5 patients, and a person of ordinary skill would not have expected the results to be applicable to the
6 general population.¹¹⁴⁹

7 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
8 person of ordinary skill would not have expected the results to be applicable to patients with
9 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
10 measurement was not feasible due to “insufficient sample.”¹¹⁵⁰ It is possible that patients with
11 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
12 calculating LDL-C levels when triglyceride level is above 400 mg/dL.¹¹⁵¹ Moreover, the study
13 does not provide different LDL-C graphs based on the baseline triglyceride levels.¹¹⁵² Therefore,
14 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
15 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
16 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
17 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
18

19
20 ¹¹⁴⁸ Takaku at ICOSAPENT_DFNDT00006897.

21 ¹¹⁴⁹ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”).

22 ¹¹⁵⁰ Takaku at ICOSAPENT_DFNDT00006884.

23 ¹¹⁵¹ See Matsuzawa at ICOSPENT_DFNDTS00006450.

24 ¹¹⁵² Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

1 times.¹¹⁵³ Because of this volatility, a person of ordinary skill would not be able to conclude
2 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
3 LDL-C, stating only that the fluctuation in LDL-C was not significant.¹¹⁵⁴

4 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
5 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
6 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
7 administration of *fish oil* to hypercholesterolemia patients.”¹¹⁵⁵ In contrast, Takaku states merely
8 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
9 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
10 was attributable to fish oil in general, not EPA specifically.

11 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
12 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
13 studies cited by Defendants suggest that EPA increases LDL-C.¹¹⁵⁶ Defendants identify no other
14 basis upon which a person of ordinary skill would have sought to combine the Omacor
15 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

16 (ii) Nozaki and/or Hayashi Do
17 Not Disclose Purported
18 Known Clinical Benefits of
Administering Pure EPA

19 Defendants contend that Nozaki and Hayashi disclose the purported known clinical
20 benefit of administering pure EPA, lowering TGs “without raising Apolipoprotein B.”¹¹⁵⁷

21 ¹¹⁵³ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

22 ¹¹⁵⁴ Takaku at ICOSAPENT_DFNDT00006897.

23 ¹¹⁵⁵ Takaku at ICOSAPENT_DFNDT00006897.

24 ¹¹⁵⁶ See, e.g., Rambjor.

¹¹⁵⁷ Defendants’ Joint Invalidity Contentions at 255.

1 Nozaki and Hayashi do not disclose or suggest “a statistically significant reduction in
2 triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B”
3 when purified EPA is administered to the very high TG patient population as the claims of the
4 ‘715 Patent require.

5 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
6 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
7 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
8 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
9 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
10 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
11 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
12 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
13 patient population were abnormally high and would not have relied upon these results. Further,
14 the person of skill in the art would not have looked to this patient population to predict the Apo-
15 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
16 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
17 levels.¹¹⁵⁸ Nozaki does not provide a motivation or reasonable expectation of success for
18 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
19 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
20 effect “a statistically significant reduction in triglycerides without effecting a statistically
21 significant increase in LDL-C or Apolipoprotein B in the subject” as the claims of the ‘715
22 Patent require.

23
24 ¹¹⁵⁸ Nozaki at 256.

1 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
2 the EPA and the DHA content in the composition that was administered is unknown. A person
3 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
4 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
5 C were not statistically significant.¹¹⁵⁹ Further, the person of skill in the art would not have
6 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
7 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
8 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
9 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
10 to effect “a statistically significant reduction in triglycerides without effecting a statistically
11 significant increase in LDL-C or Apolipoprotein B in the subject” as the claims of the ‘715
12 Patent require.

13 Further, Hayashi was a small study conducted in only Japanese patients and was not
14 placebo controlled. This study would not have been extrapolated to Western populations
15 because the Japanese diet contains much more fish and has a number of other different attributes.
16 The Japanese consume a higher amount of EPA and DHA in their diets than Western
17 populations. In fact, Defendants’ own reference states that the results from studies where the
18 patient population is exclusively Japanese cannot be generalized to other populations.¹¹⁶⁰ The
19 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
20 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
21

22 _____
23 ¹¹⁵⁹ Hayashi at 26, Table I.

24 ¹¹⁶⁰ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to other populations.”).

1 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
2 the Japanese respond differently to lipid lowering agents than Westerners.

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

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

11 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
12 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
13 C levels.”¹¹⁶¹ Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
14 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
15 rely on to support this statement does not categorize the increase in LDL-C as a “negative effect”
16 in light of the overall impact of the disclosed composition on all lipid parameters. Further, the
17 patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels.
18 As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
19 effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or
20 Maki—as in very-high TG patients because patients with higher TG levels had different lipid
21 responses compared to patients with lower TG levels. Patients with very-high TG levels were
22 considered fundamentally different from patients with borderline-high or high triglycerides from

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24 ¹¹⁶¹ Defendants’ Joint Invalidity Contentions at 258.

1 a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of
2 ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would
3 not increase LDL-C substantially in patients with normal to borderline high TG levels, but would
4 substantially increase LDL-C in patients with very high TG levels.

5 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
6 that “DHA was responsible for the increase in LDL-C levels.”¹¹⁶² The discussion related to
7 Grimsgaard in Section V.B.3.c.1.a.ii.a.i and Mori 2000 in Section V.B.3.c.1.a.i.a.iii is
8 incorporated herein by reference.

9 Defendants argue that Maki discloses the administration of purified DHA resulted in the
10 desired reduction of TGs, but also significantly increased LDL-C levels.¹¹⁶³ Maki was designed
11 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
12 below-average levels of HDL-C levels.¹¹⁶⁴ The DHA supplemented group was administered
13 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
14 monounsaturated and polyunsaturated fatty acids.¹¹⁶⁵ Therefore, Maki demonstrated that when
15 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
16 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
17 observed.¹¹⁶⁶ However, one cannot attribute the rise in LDL-C solely to DHA, because the
18 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
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20 _____
21 ¹¹⁶² Defendants’ Joint Invalidity Contentions at 256.

22 ¹¹⁶³ Defendants’ Joint Invalidity Contentions at 258-59.

23 ¹¹⁶⁴ Maki at 190.

24 ¹¹⁶⁵ Maki at 191.

¹¹⁶⁶ Maki at 195.

1 also contributed to the elevation in LDL cholesterol.”¹¹⁶⁷ Further, Maki admits that the
2 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
3 supplementation are not fully understood.”¹¹⁶⁸ Therefore, the results of Maki are inconclusive as
4 to DHA’s effect alone on LDL-C levels.

5 Defendants mischaracterize the rise in LDL-C associated with the administration of
6 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
7 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
8 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
9 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
10 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
11 less worrisome.”¹¹⁶⁹ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
12 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
13 “less worrisome” because of the “potentially favorable effects on triglycerides, the
14 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
15 particles.”¹¹⁷⁰

16 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
17 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
18 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
19 has little effect on LDL-C levels.¹¹⁷¹ Defendants identify no other basis upon which a person of
20

21 ¹¹⁶⁷ 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).

22 ¹¹⁶⁸ Maki at 197.

23 ¹¹⁶⁹ Maki at 197.

24 ¹¹⁷⁰ Maki at 197.

¹¹⁷¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
2 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

3 (iii) The '715 Patent Is Not Obvious Over the
4 Omacor PDR/Lovaza PDR, in Combination
5 with Katayama in View of Satoh and/or by
6 Satoh or Shinozaki in Further View of
7 Contacos

8 With respect to the '715 Patent, Defendants present a specific combination of five
9 references: “the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of
10 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or
11 Shinozaki in further view of Contacos.”¹¹⁷² Defendants also present charts purporting to assert
12 that an additional 60 references may be combined in order to render the Claims obvious. Not
13 only do Defendants ignore the improbability that a person of ordinary skill would combine 60
14 separate references, they additionally do not suggest any identify for combining these references.
15 Although Defendants need not point to an explicit statement in the prior art motivating the
16 combination of these references, any assertion of an “apparent reason” to combine must find a
17 basis in the factual record.¹¹⁷³ Defendants’ unsupported cobbling of selective disclosures

18 ¹¹⁷² Defendants’ Joint Invalidity Contentions at 256.

19 ¹¹⁷³ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
20 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
21 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
22 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi
23 Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
24 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

1 represents hindsight reconstruction.¹¹⁷⁴ Defendants’ contentions are no more than an assertion
2 that certain claim elements were known in the prior art. Throughout their contentions,
3 Defendants’ selectively cite to data points in a reference without considering other disclosures or
4 even the reference as a whole. Each reference, however, must be evaluated for all that it
5 teaches.¹¹⁷⁵ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

7 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
8 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
9 acid compositions or administration period. The Lovaza PDR further does not disclose a method
10 to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza
11 PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference
12 would cause a significant increase in LDL-C levels in the very high TG patient population, for
13 whom the product is indicated. At most, the Lovaza PDR discloses administration of a
14 prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an
15 adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG
16 levels.

17 Defendants formulate an obviousness argument that relies on Contacos.¹¹⁷⁶ However,
18 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
19
20

21 ¹¹⁷⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
22 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 ¹¹⁷⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ¹¹⁷⁶ *Id.*

1 element, an “apparent reason” or motivation to combine the elements in the manner claimed,¹¹⁷⁷
2 or “a reasonable expectation of success”¹¹⁷⁸ of achieving the claimed invention.

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

11 The proposed combinations do not render the independent claims of the ’715 Patent
12 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
13 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
14 and the Lovaza package insert specifically) during prosecution.¹¹⁷⁹

15 Because Defendants do not identify any combination of references, they necessarily fail
16 to offer any evidence that a person of skill in the art would be motivated to combine those
17

18 ¹¹⁷⁷ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
19 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
20 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 ¹¹⁷⁸ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
22 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

23 ¹¹⁷⁹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1 references in order to achieve the invention of the claim as a whole. Defendants have not met
2 the burden with the naked assertion that it would have been obvious to seek the claim element.

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. Defendants make a conclusory statement that there was a
7 reasonable expectation of success, without providing a support other than merely identifying
8 prior art references that purportedly disclose disparate elements.¹¹⁸⁰ The mere fact that elements
9 are capable of being physically combined does not establish reasonable expectation of
10 success.¹¹⁸¹

11 Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting
12 TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively.
13 Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per
14 day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.¹¹⁸²
15 Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient*
16 *population*, and does not provide any reasonable expectation of success in lowering TG levels in
17 the very high TG patient population without increasing LDL-C. Defendants discuss the claim
18

19 _____
20 ¹¹⁸⁰ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

22 ¹¹⁸¹ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

24 ¹¹⁸² See Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

1 elements in isolation, and fail to address the claimed invention as a whole.¹¹⁸³ Defendants
2 selectively cite to an unspecified isolated disclosure within a reference without considering other
3 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
4 that it teaches.¹¹⁸⁴ Defendants’ unsupported cobbling of selective disclosures represents
5 hindsight reconstruction.¹¹⁸⁵

6 The analysis of the independent claims of the ’715 Patent is incorporated into all asserted
7 claims that depend from those Claims.

8 (iv) A Person of Ordinary Skill Would Not Have
9 Been Motivated to Find an Omega-3 Fatty
10 Acid “therapy that Would Reduce TG
11 Levels in Patients with TG Levels \geq 500
12 mg/dL Without Negatively Impacting LDL-
13 C Levels.”

14 Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG
15 levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there
16 was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy,
17 or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels
18 for very-high TG patients at the time of the invention. A person of ordinary skill in the art
19 understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and
20 Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were
21 available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription

21 ¹¹⁸³ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ¹¹⁸⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹¹⁸⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly
 2 undesirable side effects—including “flushing” (or reddening of the face and other areas with a
 3 burning sensation) and dyspepsia—that limited their usefulness.¹¹⁸⁶ Fibrates were effective at
 4 reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG
 5 levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an
 6 LDL-C lowering medication such as a statin.¹¹⁸⁷ However, the risk of rhabdomyolysis increased
 7 five-fold if fibrates were administered with a statin.¹¹⁸⁸ Therefore, physicians were reluctant to
 8 recommend, and patients were hesitant embrace, a combination fibrate/statin course of
 9 treatment.¹¹⁸⁹ Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to
 10 fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However,
 11 Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

12 In any event, a person of ordinary skill in the art would have understood that omega 3-
 13 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
 14 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
 15 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
 16 without increasing LDL-C in very high TG patients:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients

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 18
 19
 20 ¹¹⁸⁶ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 ¹¹⁸⁷ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”).

22 ¹¹⁸⁸ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 ¹¹⁸⁹ See *Id.*, ¶ 17.

24

Fibrate ¹¹⁹⁰	-20%	+45%
Lovaza/Omacor ¹¹⁹¹	-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.”¹¹⁹² 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.¹¹⁹³

¹¹⁹⁰ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

¹¹⁹¹ Chan 2002 I at 2381 (Table 3).

¹¹⁹² Defendants’ Joint Invalidity Contentions at 258.

¹¹⁹³ 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.

1 It was well known at the time of the invention that omega-3 fatty acids, including both
2 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
3 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
4 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
5 VLDL particles to LDL.¹¹⁹⁴ A person of ordinary skill in the art understood that EPA and DHA
6 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
7 discussing the TG-lowering mechanism of omega-3 fatty acids.¹¹⁹⁵ The discussion related to the
8 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
9 incorporated herein by reference.

10 In fact, it was well understood that the degree of LDL-C elevation observed with
11 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
12 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
13 the most in patients with the highest pretreatment TG levels.¹¹⁹⁶ Therefore, a person of ordinary
14 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
15 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-
16 C was often offset by concurrent treatment with statins.¹¹⁹⁷ The safety and efficacy of using
17 prescription omega-3 in combination with a statin has been well-established.¹¹⁹⁸

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20 ¹¹⁹⁴ 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”).

21 ¹¹⁹⁵ 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)).

22 ¹¹⁹⁶ *See* Bays 2008 Rx Omega-3 p. 402.

23 ¹¹⁹⁷ *See* Harris 2008 at 14, McKenney at 722.

24 ¹¹⁹⁸ McKenney at 722-23.

1 Although an increase in LDL-C was generally observed when omega-3 fatty acids were
2 administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a
3 cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia.
4 Therefore, the final LDL-C concentration may still be in the normal range.¹¹⁹⁹ Furthermore, it
5 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.¹²⁰⁰

6 In two pivotal studies in very-high TG patients, both of which used prospective,
7 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
8 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).¹²⁰¹ Correspondingly, prescription
9 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.¹²⁰² Therefore,
10 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
11 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
12 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
13 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
14 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the

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17 ¹¹⁹⁹ See Westphal at 918, Harris 1997 at 389.

18 ¹²⁰⁰ See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals
19 with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester
20 transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he
21 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-
22 high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the
treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
decreased non-HDL-C levels (TC minus HDL-C)”).

23 ¹²⁰¹ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 ¹²⁰² McKenney 2007 at 722 (see Fig. 1).

1 number of small, dense LDL particles to larger LDL particles.¹²⁰³ Lovaza/Omacor “adversely
2 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
3 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”¹²⁰⁴

4 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
5 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
6 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
7 of [coronary heart disease].”¹²⁰⁵

8 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
9 the time of the claimed inventions would have been motivated to find a therapy that would
10 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
11 LDL-C levels,”¹²⁰⁶ one of ordinary skill in the art at the time of the invention understood that the
12 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
13 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
14 increase in very-high TG patients, and in some instances the rise was not concerning because
15 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
16 concentration would still be in the normal range. When LDL-C levels increased beyond what
17 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively
18 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
19 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
20 identify any other basis upon which a person of ordinary skill would have been motivated to find

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22 ¹²⁰³ McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 ¹²⁰⁴ Stalenhoef at 134.

24 ¹²⁰⁵ Harris 1997 at 389.

¹²⁰⁶ Defendants’ Joint Invalidation Contentions at 257-58.

1 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
2 impacting LDL-C levels.

3 Defendants make the conclusory allegation that “routine optimization” by a person of
4 ordinary skill would yield the claimed invention.¹²⁰⁷ Defendants, however, have offered no
5 explanation to support that allegation and they further fail to establish any of the required criteria
6 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
7 factual detail to support their allegation and they fail to link the allegation to any particular claim
8 or claim element. Defendants mere allegation constitute an improper placeholder to later
9 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
10 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
11 combinations alleged by Defendants and, for the same reasons, it would not be routine to
12 combine such references. Where, for example, defendants argue that it would be routine to go
13 from the high TG patient population to the very high TG patient population,¹²⁰⁸ they provide no
14 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
15 would have understood these patient populations to be distinct with different impacts of lipid
16 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
17 not have considered the dosage modification suggested by defendants to be routine; Defendants’
18 argument to the contrary represents hindsight bias.

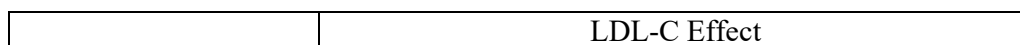
19 In addition, a person of ordinary skill would have no motivation to combine these
20 references because EPA would have been expected to have same result as the mixture of EPA
21 and DHA used in Lovaza/Omacor.

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23 ¹²⁰⁷ See, e.g., Defendants’ Joint Invalidation Contentions at 253.

24 ¹²⁰⁸ Defendants’ Joint Invalidation Contentions at 238.

(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 of 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.¹²⁰⁹ 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:



¹²⁰⁹ 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.

	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ¹²¹⁰	-20%	+45%
Lovaza/Omacor ¹²¹¹	-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.¹²¹²

Defendants’ position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to patients with very high triglyceride levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that Defendants’ provide no evidence that anyone thought to administer Epadel.¹²¹³ Epadel was available for many years prior to the invention of the ’715 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

¹²¹⁰ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

¹²¹¹ Chan 2002 I at 2381 (Table 3).

¹²¹² 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.

¹²¹³ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not examined in any study directed to the very-high TG patient population supports Amarin’s position.

1 levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration
2 of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not
3 expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as
4 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
5 triglycerides.

6 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
7 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
8 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
9 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
10 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.¹²¹⁴
11 Defendants' contentions are no more than a demonstration that certain claim elements was
12 known in the prior art and demonstrates impermissible hindsight reconstruction.¹²¹⁵ As is
13 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,
14 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA
15 and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that
16 administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,
17 none of these references would provide a person of ordinary skill in the art with a reasonable
18 expectation of successfully obtaining the claimed invention even if there were reasons to
19 combine disparate, independent elements found in the prior art, which there were not.

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22 ¹²¹⁴ Defendants' Joint Invalidity Contentions at 260.

23 ¹²¹⁵ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
24 KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.").

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

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P [†]	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 [‡]	-0.22 ± 0.31 [‡]	1.23 ± 0.57	-0.15 ± 0.40 [‡]	1.22 ± 0.55	0.11 ± 0.34 [‡]	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 [‡]	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 [‡]	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 [‡]	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 [‡]	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 [‡]	0.96 ± 0.13	0.04 ± 0.08 [‡]	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 [‡]	4.70 ± 1.24	-0.13 ± 0.47 [‡]	4.43 ± 1.19	0.11 ± 0.62	0.002	0.4	0.0006	0.007

[†] ANOVA for between-group comparisons of change.

[‡] x ± SD.

^{‡-‡} One-sample t test of difference between baseline and 7 wk: [‡] P < 0.001, [‡] P < 0.01, [‡] P < 0.05.

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

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

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

Defendants argue that it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. However, the

1 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-
2 try” proves that the claimed invention was obvious where the prior art did not suggest what to
3 try.¹²¹⁶ Rather than there being a limited number of options, the state of the art provided a
4 plethora of compositions and administration protocols associated with multiple kinds of TG-
5 lowering therapies.¹²¹⁷ There were not a finite number of options for a person of ordinary skill
6 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
7 population.

8 Defendants argue that a person of ordinary skill at the time of the invention, based on
9 studies in normal, borderline-high and high TG patients, knew that administration of DHA alone
10 resulted in undesirable increased LDL-C levels while administration of EPA alone had little to
11 no impact on LDL-C levels.¹²¹⁸ However, that statement does not conform with what was
12 known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high
13 TG patients. Instead as Defendants’ own prior art demonstrates, Epadel and Lovaza/Omacor
14 were both known to have little or no effect on LDL-C in patients with borderline-high/high TG
15 levels.

16 Further, a person of ordinary skill in the art would have understood that EPA therapy
17 would *not* reduce Apo-B¹²¹⁹ (which is a reflection of total atherogenic lipoproteins)¹²²⁰ in very
18 high TG patients, and accordingly would not have had a reasonable expectation of success in
19 achieving the claimed invention (including its Apo-B effects) by administering the claimed EPA

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21 ¹²¹⁶ See *Sanofi*, 748 F.3d at 1360–61.

22 ¹²¹⁷ See *supra* Section III.

23 ¹²¹⁸ Defendants’ Joint Invalidity Contentions at 259.

24 ¹²¹⁹ see Section V.O.

¹²²⁰ see Section III.

1 composition to the very high TG patient population. Indeed, Defendants assert that “as DHA
2 was known to increase LDL-C, and as ApoB is a component of LDL-C, one of ordinary skill in
3 the art would also reasonably expect that DHA causes an increase in ApoB.”¹²²¹ But Defendants
4 provide no explanation as to why a person of ordinary skill in the art would reasonably expect
5 EPA to differ from DHA and cause a reduction in ApoB.

6 With the lack of any reasonable expectation of success, Defendants argue that their
7 proposed combination amounts to a simple substitution of one known element for another, and
8 that that these changes yield predictable results.¹²²² Such an argument, however, represents pure
9 and impermissible hindsight bias and further does not consider that reasons for which a person of
10 ordinary skill would not be motivated to combine these references and affirmatives ways in
11 which the art taught away from these combinations.

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

14 (i) The ‘715 Patent is not Obvious Over WO
15 ‘118 or WO ‘900, in Combination with the
Lovaza PDR, and Further in View of Leigh-
16 Firbank and/or Mori 2000

17 With respect to the ‘715 Patent, Defendants present a combination of five references:
18 “WO ‘118 or WO ‘900, in combination with treatment regimen of Lovaza as evidenced by the
19 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”¹²²³ Defendants also
20 present charts arguing that an additional 61 references may be combined in order to render the
21 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill

22 ¹²²¹ Defendants’ Joint Invalidity Contentions at 273.

23 ¹²²² Defendants’ Joint Invalidity Contentions at 261.

24 ¹²²³ Defendants’ Joint Invalidity Contentions at 263.

1 would combine 61 separate references, they additionally do not identify any motivation for
2 combining these references.^{1224, 1225} Although Defendants need not point to an explicit statement
3 in the prior art motivating the combination of these references, any assertion of an “apparent
4 reason” to combine must find a basis in the factual record.¹²²⁶ Defendants’ unsupported cobbling
5 of selective disclosures represents hindsight reconstruction.¹²²⁷ Defendants’ contentions are no
6 more than an assertion that certain claim elements were known in the prior art. Throughout their
7 contentions, Defendants’ selectively cite to data points in a reference without considering other
8

9
10 ¹²²⁴ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more the references cited in
11 V.B.3 and 4, including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi, Katayama,
12 Matsuzawa, Mataka, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki,
13 Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-
14 Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald in combination with the knowledge of a person of
15 ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor” similarly fails to meet the
16 disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these
17 references. *See* Defendants’ Joint Invalidation Contentions at 262.

18 ¹²²⁵ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
19 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
20 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
21 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
22 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidation Contentions at 254.

24 ¹²²⁶ *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).

¹²²⁷ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
2 that it teaches.¹²²⁸ Accordingly, Defendants fail to meet their burden to establish *prima facie*
3 obviousness.

4 WO '118 is directed at the composition containing EPA for the purpose of preventing the
5 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118
6 is directed, "in particular, [to] preventing occurrence of cardiovascular events in
7 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
8 risk of the cardiovascular events."¹²²⁹ Contrary to Defendants' assertion that WO '118 discloses
9 "the administration of 4 g of pure EPA with no DHA,"¹²³⁰ WO '118 fails to disclose the claimed
10 subject with the specified very high TG levels (500-1500 mg/dL) who does not receive
11 concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified
12 fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction
13 without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of
14 possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in
15 the disclosed composition.¹²³¹

16 WO '118 does not disclose administration of highly-purified ethyl-EPA to the target
17 population of the claimed invention. The asserted claims are directed to persons with severe
18 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only
19 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.¹²³² WO

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21 ¹²²⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

22 ¹²²⁹ WO '118 at 9.

23 ¹²³⁰ Defendants' Joint Invalidation Contentions at 263.

24 ¹²³¹ WO '118 at 22-23.

¹²³² WO '118 at 8.

1 '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to
2 patients with borderline-high to high TG levels, since the primary goal for patients with very-
3 high TG is to prevent acute pancreatitis by decreasing TG levels.¹²³³

4 WO '118 also does not distinguish EPA from DHA in its disclosures regarding the
5 effectiveness of the substances for treating hypertriglyceridemia.¹²³⁴ WO '118 states that
6 "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-
7 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
8 DHA-E) are not particularly limited as long as intended effects of the present invention are
9 attained."¹²³⁵ It further states that "the composition is preferably the one having a high purity of
10 EPA-E and DHA-E."¹²³⁶ Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C,
11 Apo-B, or Lp-PLA2.

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

21 ¹²³³ See Section III.

22 ¹²³⁴ WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective
component").

23 ¹²³⁵ WO '118 at 22-23.

24 ¹²³⁶ WO '118 at 23.

1 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It
2 lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one
3 of them.¹²³⁷ Moreover, WO '900 does not teach the desired effect of EPA other than
4 commenting generally that it “may promote health and ameliorate or even reverse the effects of a
5 range of common diseases.”¹²³⁸ It has no discussion, for example, on any TG-lowering effect of
6 EPA. Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the
7 *specific* undesired effect of DHA or other impurities it is trying to prevent other than
8 commenting generally that “the desired effects of EPA may be limited or reversed” by them.¹²³⁹
9 It has no discussion related to any LDL-C effects caused by DHA.

10 The proposed combination does not render the independent claims of the '715 Patent
11 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
12 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
13 insert specifically) during prosecution.¹²⁴⁰

14 The analysis of the independent claims of the '715 patent is incorporated into all asserted
15 claims that depend from this Claim.

16 (a) Leigh-Firbank and Mori 2000 Do
17 Not Disclose Purported Knowledge
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20 ¹²³⁷ See, e.g., '900 Pub. at 16-17.

21 ¹²³⁸ '900 Pub. at 5.

22 ¹²³⁹ '900 Pub. at 39.

23 ¹²⁴⁰ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

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

3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
5 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
6 C levels as evidenced by Leigh-Firbank or Mori 2000.”¹²⁴¹

7 Defendants fail to identify a specific motivation to combine WO ‘118 or WO ‘900 with
8 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
9 not point to an explicit statement in the prior art motivating the combination of these references,
10 any assertion of an “apparent reason” to combine must find a basis in the factual record.¹²⁴²

11 Defendants’ unsupported cobbling of selective disclosures represents hindsight
12 reconstruction.¹²⁴³ Defendants’ contentions are no more than an assertion that certain claim
13 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
14 establish *prima facie* obviousness.

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¹²⁴¹ Defendants’ Joint Invalidity Contentions at 263.

17 ¹²⁴² See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
18 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
19 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
20 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
24 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).

¹²⁴³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

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

14 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
15 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
16 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
17 effect on LDL-C levels.¹²⁴⁴ Defendants identify no other basis upon which a person of ordinary
18 skill would have sought to combine WO ‘118, WO ‘900, the Lovaza PDR, Leigh-Firbank and/or
19 Mori.

- 20 (ii) The ‘715 Patent is not Obvious Over WO
21 ‘118, WO ‘900, Grimsgaard, Mori 2000
22 and/or Maki in Combination with the
23 Omacor PDR/Lovaza PDR, and Further in

24 ¹²⁴⁴ See *e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

With respect to the '715 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.”¹²⁴⁵ 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.¹²⁴⁶ Defendants’ unsupported cobbling of selective disclosures represents hindsight reconstruction.¹²⁴⁷ Defendants’ contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions,

¹²⁴⁵ Defendants’ Joint Invalidity Contentions at 263.

¹²⁴⁶ 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).

¹²⁴⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 Defendants’ selectively cite to data points in a reference without considering other disclosures or
2 even the reference as a whole. Each reference, however, must be evaluated for all that it
3 teaches.¹²⁴⁸ Accordingly, Defendants fail to meet their burden to establish *prima facie*
4 obviousness.

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

14 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
15 to use EPA as described in WO ’118, WO ‘900, Grimsgaard or Mori 2000 in the treatment
16 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
17 assertions fail to provide a motivation for combining the references.¹²⁴⁹ Although Defendants
18 need not point to an explicit statement in the prior art motivating the combination of these
19 references, any assertion of an “apparent reason” to combine must find a basis in the factual
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23 ¹²⁴⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ¹²⁴⁹ Defendants’ Joint Invalidity Contentions at 263.

1 record.¹²⁵⁰ Defendants’ assertions related to motivation are insufficient,¹²⁵¹ and accordingly
2 Defendants fail to meet their burden to establish *prima facie* obviousness.

3 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
4 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
5 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
6 manner claimed,¹²⁵² or “a reasonable expectation of success”¹²⁵³ of achieving the claimed
7 invention. Therefore, Defendants should be precluded from relying on this these references.

8 As discussed above in Section V.B.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
9 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
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12 ¹²⁵⁰ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
13 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
14 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
15 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
16 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
17 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
18 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
19 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
20 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
21 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
22 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
23 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

17 ¹²⁵¹ For example, Defendants’ assertion that “WO ’118 may be combined with other prior art in the field of treating
18 hypertriglyceridemia” is nothing more than a statement that a reference can be combined but fails to provide any
19 basis for that statement. While the paragraph associated with that statement makes assertions regarding the
20 disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO
21 ’118. See Defendants’ Joint Invalidity Contentions at 264.

20 ¹²⁵² *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
23 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

22 ¹²⁵³ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
23 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
24 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
2 purified EPA to the very high TG patient population and do not provide any reasonable
3 expectation of success in lowering TG levels in the very high TG patient population without
4 increasing LDL-C. As discussed above in Section V.B.3.c.1.a.ii.a.i, Takaku candidly
5 acknowledges that “only a few subjects were examined” and cautions against drawing a
6 conclusion “only from the results of the present study.”¹²⁵⁴ Further, the study did not include any
7 placebo control, therefore, a person of ordinary skill in the art would understand these reports do
8 not provide the ability to conclude that the observed lipid effects would have occurred
9 independent of the drug that is administered. In addition, the study was conducted exclusively in
10 Japanese patients, and a person of ordinary skill would not have expected the results to be
11 applicable to the general population.¹²⁵⁵

12 The proposed combination does not render the independent claims of the '715 Patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.¹²⁵⁶

16 The analysis of the independent claims of the '715 patent is incorporated into all asserted
17 claims that depend from this Claim.

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

21 ¹²⁵⁴ Takaku at ICOSAPENT_DFNDT00006897.

22 ¹²⁵⁵ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.”)

23 ¹²⁵⁶ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).
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3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
7 Maki.”¹²⁵⁷

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
10 Mori 2000 and/or Maki in Section V.B.3.c.1.a.ii.a.iii is incorporated herein by reference. A
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
15 disclose administration of DHA to the requisite patient population and teaches that DHA is
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
18 would consider. Most controlled studies in patients with normal to high baseline TG levels
19 indicated that DHA had little or no effect on LDL-C.¹²⁵⁸ Therefore, a person of ordinary skill
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 ¹²⁵⁷ Defendants’ Joint Invalidity Contentions at 264.

23 ¹²⁵⁸ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG
2 levels, a significant increase in LDL-C is observed.¹²⁵⁹ However, one of ordinary skill in the art
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.¹²⁶⁰
4 Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
8 has little effect on LDL-C levels.¹²⁶¹ Defendants identify no other basis upon which a person of
9 ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki,
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

15 For an invention to be obvious, there must have been an "apparent reason" to make it.
16 Defendants assert that a "person of ordinary skill in the art would have been motivated to
17 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
18 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."¹²⁶² However, as
19 set forth below, Defendants fail to address why a person of ordinary skill in the art would have
20 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

21 ¹²⁵⁹ Maki at 195.

22 ¹²⁶⁰ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 ("A number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated fat and cholesterol, both of which are known to elevate LDL-C.").

23 ¹²⁶¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ¹²⁶² Defendants' Joint Invalidity Contentions at 262.

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

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

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ¹²⁶³	-20%	+45%
Lovaza/Omacor ¹²⁶⁴	-6%	+45%

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

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

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23 ¹²⁶³ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ¹²⁶⁴ Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
3 purified ethyl-EPA.”¹²⁶⁵ Both of the “reasons” identified by Defendants are false.

4 Regarding Defendants’ first reason, that “products containing DHA were reported to
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
7 LDL-C.¹²⁶⁶ Therefore, a person of ordinary skill would not have concluded that DHA increases
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,
10 while EPA does not.”¹²⁶⁷ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
11 alone because it did not administer EPA and DHA separately.¹²⁶⁸ A person of ordinary skill
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
14 on lipid parameters. Second, Kelley administered DHA-rich oil that contained other saturated
15 and polyunsaturated fatty acids.¹²⁶⁹ Therefore, a person of ordinary skill would have known it is
16 unsuitable for evaluating the independent effects of DHA because it is not clear how much of the
17 supplement’s effects can be attributed to DHA.¹²⁷⁰ Kelley does not show that DHA is

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¹²⁶⁵ Defendants’ Joint Invalidation Contentions at 264-65.

20 ¹²⁶⁶ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
21 controlled, found an increase in LDL-C after DHA administration.

22 ¹²⁶⁷ Defendants’ Joint Invalidation Contentions at 269.

23 ¹²⁶⁸ The discussion related to Leigh-Firbank in Section V.A.3.c.1.a.i.a.iii is incorporated herein by reference.

24 ¹²⁶⁹ The discussion related to Kelley in Section V.A.3.c.1.a.iii.a.ii is incorporated herein by reference.

¹²⁷⁰ See Mori 2006 at 96.

1 responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general
2 phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was
3 induced by fibrate therapy.¹²⁷¹ Kelley specifically teaches that the increase in LDL-C caused by
4 DHA supplementation is unlikely to be “detrimental” because there was not a parallel increase in
5 overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a
6 rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA
7 had uniquely beneficial cardioprotective effects.¹²⁷² Finally, Theobald also does not teach that
8 DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in
9 patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when
10 compared to placebo. However, the DHA composition that was administered in Theobald
11 contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic
12 acid. Therefore, a person of ordinary skill would have known that the DHA administered by
13 Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to
14 determine whether or how much of the supplement’s effects can be attributed to
15 DHA.¹²⁷³ Contrary to Defendants’ assertion that there was “a reported advantage to using EPA
16 vs. DHA in hypertriglyceridemic subjects,”¹²⁷⁴ there was no known advantage to using EPA vs.
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after
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20 ¹²⁷¹ Kelley at 329.

21 ¹²⁷² Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”
and that “DHA supplementation may improve cardiovascular health.”)

23 ¹²⁷³ See Mori 2006 at 96.

24 ¹²⁷⁴ Defendants’ Joint Invalidation Contentions at 264.

1 EPA supplementation.”¹²⁷⁵ In addition, a person of ordinary skill would have recognized any
2 impact of DHA reported by the study to be applicable to EPA because they would have
3 understood these substances to function by the same mechanism. Furthermore, as discussed
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
6 because patients with higher TG levels had different lipid responses compared to patients with
7 lower TG levels.

8 Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in
9 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”
10 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
11 well documented.¹²⁷⁶ Lovaza/Omacor has been shown to reduce the risk for cardiovascular
12 death plus nonfatal myocardial infarction and nonfatal stroke.¹²⁷⁷ Omega-3 fatty acids have been
13 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
14 prevention trials.¹²⁷⁸ Omega-3 fatty acids were known to reduce TG concentration, have
15 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
16 and/or reduce heart rate.¹²⁷⁹

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19 ¹²⁷⁵ Mori 2000 at 1092.

20 ¹²⁷⁶ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 ¹²⁷⁷ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

22 ¹²⁷⁸ Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 Atherosclerosis 12, 13 (2008) (“Harris 2008”).

23 ¹²⁷⁹ Harris 2008 at 13.
24

1 Defendants argue that a “person of ordinary skill in the art would have appreciated the
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”¹²⁸⁰ As
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
6 and Lovaza/Omacor have been well documented.¹²⁸¹

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that
9 DHA is *more* cardioprotective than EPA.¹²⁸² This study found that “depressed levels of long-
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
11 heart disease events.”¹²⁸³ Further, the study found that DHA levels, with or without EPA, were
12 significantly lower in fatal endpoints.¹²⁸⁴ This study suggests that DHA is preferable to EPA—
13 thus teaching away from the claimed invention.¹²⁸⁵ Defendants rely on hindsight bias to argue
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
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16 ¹²⁸⁰ Defendants’ Joint Invalidity Contentions at 265.

17 ¹²⁸¹ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
18 and CHD risk.”) (“Harris 2007”).

19 ¹²⁸² Harris 2007 at 8.

20 ¹²⁸³ *Id.*

21 ¹²⁸⁴ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 ¹²⁸⁵ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *W.L. Gore & Assocs.,
Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the
prior art ... is strong evidence of nonobviousness.”).

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

3 Defendants argue that the following claim elements were known: the administration of
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
6 patients with high and very high TG levels who were not receiving concurrent lipid altering
7 therapy, and the dose of 4g/day and 12-week regimen.¹²⁸⁶ Defendants then argue that the “only
8 question is whether one skilled in the art would have been motivated to use the DHA-free,
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
10 least 500 mg/dL as part of the claimed dosage regimen.”¹²⁸⁷

11 Defendants’ contentions are no more than a recitation that certain claim elements were
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight
13 reconstruction.¹²⁸⁸ Notably, Defendants *do not* assert that a person of ordinary skill would have
14 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,¹²⁸⁹
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
17 number of prior art references disclosed the administration of purified EPA to patients with TG
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¹²⁸⁶ Defendants’ Joint Invalidity Contentions at 267.

21 ¹²⁸⁷ Defendants’ Joint Invalidity Contentions at 267.

22 ¹²⁸⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 ¹²⁸⁹ Nakamura, Matsuzawa, and Takaku.

1 levels > 500 mg/dL.”^{1290, 1291} The disclosures of Nakamura (one patient), Matsuzawa (disclosure
2 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the
3 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of
4 ordinary skill in the art would *not* understand these references to relate to the use of EPA in
5 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions
6 regarding these references in terms of the very high TG patient population. In Nakamura, one
7 patient had a baseline TG level > 500 mg/dL.¹²⁹² However, the mean baseline TG for all patients
8 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was
9 well below 500 mg/dL.¹²⁹³ In Matsuzawa, three patients had TG levels between 400 and 1000
10 mg/dL and one patient had TG levels > 1,000 mg/dL.¹²⁹⁴ Based on this disclosure, only one
11 patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one patient was excluded
12 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol
13 made it impossible to assess triglyceride levels.”¹²⁹⁵ In Takaku, three patients had baseline TG
14 levels above 500 mg/dL.¹²⁹⁶ However, the mean baseline TG level for all patients was 245
15 mg/dL.¹²⁹⁷ Indeed, the mean baseline TG level of the patients in all three studies was well below
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17 ¹²⁹⁰ Defendants’ Joint Invalidity Contentions at 266.

18 ¹²⁹¹ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumura specifically
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 ¹²⁹² Nakamura at 23, Table 1.

23 ¹²⁹³ Nakamura at 23, Tables 1 and 2.

24 ¹²⁹⁴ *Id.* at 23.

¹²⁹⁵ *Id.* at 10.

¹²⁹⁶ Takaku at ICOSAPENT_DFNDTS00006895.

¹²⁹⁷ Takaku at ICOSAPENT_DFNDTS00006875.

1 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be
2 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,
3 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the
4 Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.¹²⁹⁸
5 Defendants have failed to identify all of the claimed elements and fail to provide motivation to
6 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with
7 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated
9 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
10 known TG-lowering effects of highly-purified EPA-E."¹²⁹⁹ This argument is flawed. The prior
11 art demonstrates a wide range of administration periods utilized in different clinical studies. For
12 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
13 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
14 Given the large number of choices of administration periods disclosed in prior art, Defendants
15 have not shown that a person of ordinary skill would not have been motivated to administer
16 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

17 Moreover, a person of ordinary skill would not have been motivated to administer highly-
18 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
19 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
20 triglycerides.¹³⁰⁰ In fact, Defendants acknowledge in their Joint Invalidation Contentions that

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22 ¹²⁹⁸ See Matsuzawa at ICOSAPENT_DFNDTS00006450.

23 ¹²⁹⁹ Defendants' Joint Invalidation Contentions at 267.

24 ¹³⁰⁰ Mori 2006 at 98.

1 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
2 another.”¹³⁰¹ Data from some studies even suggested that DHA or fish oil may reduce
3 triglyceride more effectively than EPA.¹³⁰² Therefore, a person of ordinary skill would not have
4 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
5 of EPA and DHA (such as Lovaza) for 12 weeks.

6 Defendants argue that a “person of ordinary skill in the art also would have been
7 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
8 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.¹³⁰³ This
9 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
10 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
11 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

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

15 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
16 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
17 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
18 dose of 4 g/day rather than a lower dose.”¹³⁰⁴ A person of ordinary skill would not have relied
19 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
20

21 ¹³⁰¹ Defendants’ Joint Invalidation Contentions at 271.

22 ¹³⁰² Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
23 grater with DHA supplementation than EPA supplementation).

24 ¹³⁰³ Defendants’ Joint Invalidation Contentions at 267.

¹³⁰⁴ Defendants’ Joint Invalidation Contentions at 268.

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

4 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
5 triglycerides.¹³⁰⁵ Therefore, a person of ordinary skill would not have been motivated to
6 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
7 EPA and DHA (such as Lovaza).

8 Defendants further argue that a “person of ordinary skill in the art would have also been
9 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
10 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
11 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
12 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”¹³⁰⁶ This
13 argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a
14 greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill
15 would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any
16 other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects
17 having baseline TG levels above 500 mg/dL. Further, a person of ordinary skill would have
18 expected that a greater decrease in TG levels, in the very high TG patient population, would lead
19 to a greater increase in LDL-C levels.

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

22 _____
23 ¹³⁰⁵ See Section III.

24 ¹³⁰⁶ Defendants’ Joint Invalidity Contentions at 268.

1 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
2 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”¹³⁰⁷ Defendants first
3 support this argument by asserting that a person of ordinary skill in the art would have known
4 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
5 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
6 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
7 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
8 V.B.4. and 5” to support this proposition,¹³⁰⁸ however these references do not disclose or suggest
9 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
10 high TG patients.¹³⁰⁹

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

16 Defendants argue that a person of ordinary skill in the art “would have known that an
17 increase in LDL-C was an adverse health effect to be avoided.”¹³¹⁰ While an increase in LDL-C
18 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
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20

21 ¹³⁰⁷ Defendants’ Joint Invalidation Contentions at 269.

22 ¹³⁰⁸ Defendants’ Joint Invalidation Contentions at 269.

23 ¹³⁰⁹ *See* Section IV.

24 ¹³¹⁰ Defendants’ Joint Invalidation Contentions at 271.

1 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
2 fatty acids generally, was related to increased conversion of VLDL to LDL particles.¹³¹¹

3 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the
4 art would have been motivated, with a reasonable expectation of success, to administer a highly-
5 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in
6 LDL-C with DHA.”¹³¹² However, a person of ordinary skill in the art expected an increase in
7 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
8 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
9 decrease in the production of VLDL particles and a significant increase in the conversion of
10 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
11 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.¹³¹³ A
12 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
13 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
14 mechanism of omega-3 fatty acids.¹³¹⁴ The discussion related to the TG-lowering mechanism of
15 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

16 Accordingly, a person of ordinary skill would not have been motivated to combine WO
17 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
18 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
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20 ¹³¹¹ See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
23 levels when given prescription omega-3 therapy”); Chan 2003.

22 ¹³¹² Defendants’ Joint Invalidity Contentions at 271.

23 ¹³¹³ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
24 decrease in VLDLs after n-3 fatty acid treatment”).

24 ¹³¹⁴ Bays 2008 I, at 398; Bays *in* Kwiterovich at 247.

1 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
2 Firbank and/or Mori 2000.

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

7 Defendants contend that a “person of ordinary skill in the art would have been motivated
8 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal
9 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”¹³¹⁵

10 Defendants also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . .
11 would have given a person of ordinary skill in the art a reasonable expectation of successfully
12 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
13 these subjects relative to baseline or placebo.”¹³¹⁶ However, Defendants provide no evidence
14 that a person of ordinary skill would have had a reasonable expectation of success in a method of
15 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
16 EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore,
17 Defendants fail to provide a reasonable expectation of success for the claimed invention.

18 Defendants further argue, that “because it was known that DHA and EPA were
19 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
20 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
21 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been
22 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition

23 ¹³¹⁵ Defendants’ Joint Invalidity Contentions at 264.

24 ¹³¹⁶ Defendants’ Joint Invalidity Contentions at 268.

1 with a reasonable expectation of success that such administration would result in reducing
2 triglycerides while avoiding an increase in LDL.”¹³¹⁷ Defendants argument is without any basis.
3 To the contrary, because a person of ordinary skill in the art would have understood DHA and
4 EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have
5 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
6 explanation and cite to no article to support their argument that the similar effects on TG levels is
7 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
8 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
9 both EPA and DHA, whether administered alone or in combination, would cause an increase in
10 LDL-C when administered to the very high TG patient population.

11 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
12 with very-high TG. A person of ordinary skill would have thus expected EPA, like
13 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
14 population. It was well known that TG-lowering agents, specifically fibrates and
15 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
16 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
17 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
18 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
19 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
20 reflected in the prior art:



23 ¹³¹⁷ Defendants’ Joint Invalidity Contentions at 272.

24

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	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ¹³¹⁸	-20%	+45%
Lovaza/Omacor ¹³¹⁹	-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 administering purified EPA to the requisite patient population to achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel, which was available for many years prior to the invention of the '715 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

¹³¹⁸ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

¹³¹⁹ Chan 2002 I at 2381 (Table 3).

1 Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high
2 triglycerides.

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

5 (2) Dependent Claims

6 (a) Defendants Have Not Shown that Claims 2, 3, 12,
7 16, and 19 of the '715 Patent Would Have Been
Obvious

8 Plaintiffs incorporate by reference the discussion related to the independent claims in
9 Section V.B.3. Because Defendants have not shown the obviousness of the independent claims
10 by clear and convincing evidence, they also have not adequately proven the obviousness of
11 Claims 2, 3, 12, 16, and 19.

12 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach
13 the additional claim elements of dependent Claims 2 and 3. Defendants contend, without
14 providing any support, that the claim elements are the results of simply optimizing the conditions
15 described in the prior art and within the purview of the skilled physicians. These contentions: 1)
16 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant
17 to an obvious analysis; 3) fail to address whether the specific combination of claim elements
18 were all present in the prior art references that would have been combined by a person of
19 ordinary skill in the art to produce the claimed invention with a reasonable expectation of
20 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
21 analysis, but trivialize the claim element to the point of reading the element out of the claim.
22 Although convenient and expedient, Defendants' approach does not conform with the Local
23 Patent Rules of this District, the law of claim construction, or the law of obviousness.

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1 Defendants fail to show a specific combination of references that discloses each element
2 of the claimed invention. None of the cited references discloses administration of the claimed
3 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
4 combined to teach the administration of the claimed EPA to very high TG patients.¹³²⁰
5 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
6 considering other disclosures or even the reference as a whole. Each reference, however, must
7 be evaluated for all that it teaches.¹³²¹ Defendants’ unsupported cobbling of selective disclosures
8 represents hindsight reconstruction.¹³²²

9 Defendants fail to show a motivation or reason to combine or modify the references
10 recited above. Defendants make a conclusory statement that the claimed methods of treatment
11 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not
12 show why a person of ordinary skill would have been motivated to combine the references to
13 achieve the claimed invention.¹³²³

14 Defendants fail to show a reasonable expectation that a person of ordinary skill would
15 have successfully achieved the claimed invention. In fact, other than simply identifying prior art
16

17 _____
18 ¹³²⁰ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 ¹³²¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ¹³²² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ¹³²³ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
23 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 references that purportedly disclose disparate elements, Defendants do not even discuss whether
2 a person of ordinary skill would have expected that the combination to work for its intended
3 purpose.¹³²⁴ As such, Defendants fail to demonstrate reasonable expectation of success of the
4 claimed invention.

5 (b) Defendants Have Not Shown that Claim 4 of the
6 '715 Patent Would Have Been Obvious.

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

11 Defendants offer no reference in support of their contention that this claim is obvious.
12 Defendants contend, without providing any support, that it would be obvious to one of skill in
13 the art to administer a composition containing EPA, but containing no DHA, with a reasonable
14 expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These
15 contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art;
16 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of
17 claim elements were all present in the prior art references that would have been combined by a
18 person of ordinary skill in the art to produce the claimed invention with a reasonable expectation
19 of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
20 analysis, but trivialize the claim element to the point of reading the element out of the claim.

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23 ¹³²⁴ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Although convenient and expedient, Defendants’ approach does not conform with the Local
2 Patent Rules of this District, the law of claim construction, or the law of obviousness.

3 Defendants fail to show a specific combination of references that discloses each element
4 of the claimed invention. None of the cited references discloses administration of the claimed
5 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
6 combined to teach the administration of the claimed EPA to very high TG patients.¹³²⁵
7 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
8 considering other disclosures or even the reference as a whole. Each reference, however, must
9 be evaluated for all that it teaches.¹³²⁶ Defendants’ unsupported cobbling of selective disclosures
10 represents hindsight reconstruction.¹³²⁷

11 Defendants fail to show a motivation or reason to combine or modify the references
12 recited above. Defendants make a conclusory statement that the claimed methods of treatment
13 would have been obvious but such a naked assertion does not show why a person of ordinary
14 skill would have been motivated to combine the references to achieve the claimed invention.¹³²⁸

17
18 ¹³²⁵ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 ¹³²⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ¹³²⁷ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ¹³²⁸ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
23 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 Defendants fail to show a reasonable expectation that a person of ordinary skill would
2 have successfully achieved the claimed invention. In fact, Defendants do not even discuss
3 whether a person of ordinary skill would have expected that the combination to work for its
4 intended purpose.¹³²⁹ As such, Defendants fail to demonstrate reasonable expectation of success
5 of the claimed invention.

6 Defendants cite only one reference in their invalidity contentions with respect to this
7 claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead,
8 Defendants cite Theobald for the proposition that “it was known that Apo-B is a component of
9 LDL-C.” Defendants cite to no passage or page of Theobald in connection with that argument
10 and no support for their argument that Theobald makes such a disclosure. Defendants appear to
11 suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all
12 atherogenic lipoproteins.¹³³⁰

13 Defendants then make the unsupported assertion that “one of ordinary skill in the art
14 would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to
15 reduce VLDL syntheses.” They are incorrect. Neither Defendants’ characterization of Theobald
16 nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render
17 this claim obvious. Defendants’ assertion that EPA was known to reduce VLDL synthesis
18 ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL
19 synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with
20 respect to this claim or Apo-B levels.

22 ¹³²⁹ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

24 ¹³³⁰ June 26, 2012 Bays Declaration; *see also* Section III.

As discussed above, *see* Section IV, Theobald discloses the administration of a triacylglycerol composition derived from *Cryptocodinium cohnii* to healthy subjects. While Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a component of LDL-C, they fail to discuss the reference’s disclosures regarding the impact of administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference.¹³³¹

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

	DHA		Placebo		Treatment effect ¹
	Before treatment	After treatment	Before treatment	After treatment	
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 $\bar{x} \pm \text{SEM}$ (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.

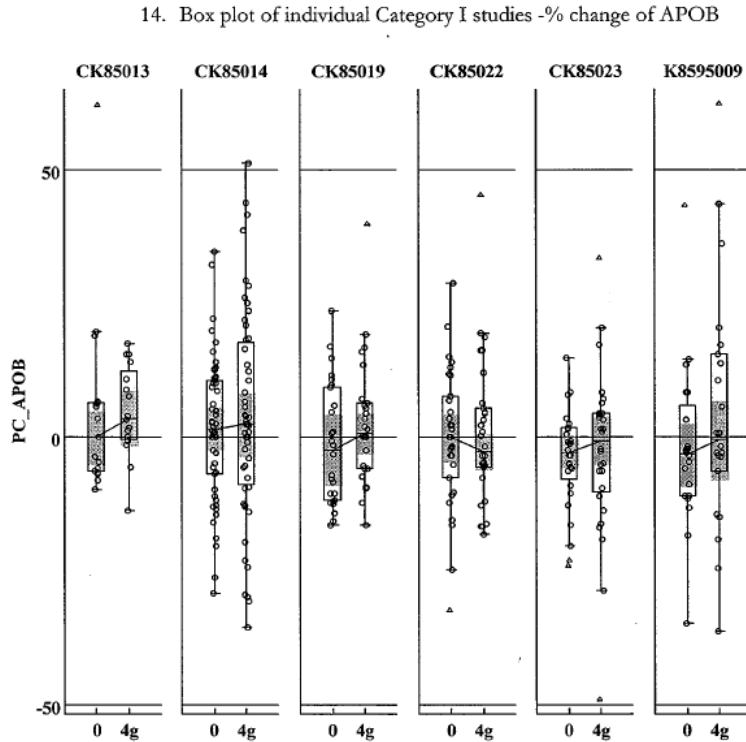
⁸ Weight increased over the entire study period. Significant order × time effect, $P = 0.001$.

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

¹³³¹ Theobald at 561, table 3.

1 Apo-B levels in patients with very high TG levels.¹³³² The Lovaza clinical trial, which was a
2 large study conducted on patients with very high TG levels, shows no difference between a
3 placebo-control group and the treatment group with respect to Apo-B levels.¹³³³



16

17 In each of these studies, including K8595009, where subjects had a median baseline TG
18 level of 818 mg/dL,¹³³⁴ there was no change in Apo-B between the control and treatment groups.
19 Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected
20 that treatment with Lovaza did not impact Apo-B compared to placebo.¹³³⁵

21

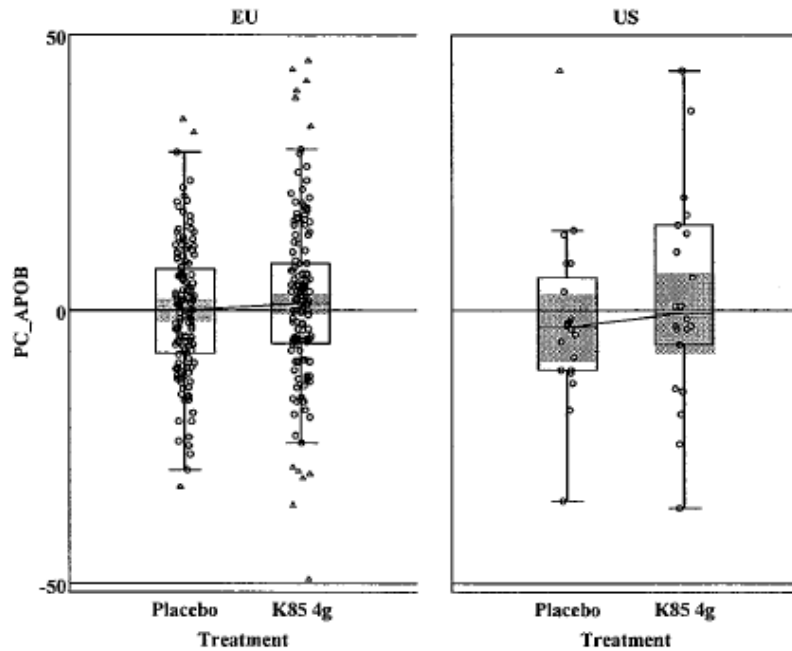
22 ¹³³² May 8, 2012 Bays Declaration.

23 ¹³³³ Lovaza Approval Package at Table 14.

24 ¹³³⁴ The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

¹³³⁵ 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.¹³³⁶ 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

¹³³⁶ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

1 those references, also reflecting a lack of motivation and no reasonable expectation of
2 success.¹³³⁷

3 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
4 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.¹³³⁸ The person of
5 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
6 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
7 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
8 lipoproteins, but instead smaller, denser particles referred to as remnant.¹³³⁹ Accordingly,
9 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
10 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
11 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
12 would not significantly impact Apo-B.

13 Accordingly, a person of ordinary skill in the art would not have been motivated to
14 replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art
15 have been motivated to administer the EPA composition of the claimed invention to very high
16 TG patients. For the same reasons, a person of ordinary skill in the art would not have a
17 reasonable expectation of success in achieving the claimed invention.
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¹³³⁷ Defendants' Contentions at 236.

23 ¹³³⁸ ATP-III at 3170; Bays 2008 I at 395.

24 ¹³³⁹ Kwiterovich in Kwiterovich at 4.

1 (c) Defendants Have Not Shown that Claim 5 of the
2 '715 Patent Would Have Been Obvious

3 Plaintiffs incorporate by reference the discussion related to the independent claims in
4 Section V.B.3. Because Defendants have not shown the obviousness of Claim 1 by clear and
5 convincing evidence, they also have not adequately proven the obviousness of Claim 5.

6 Defendants contend, without support, that the recited reduction in TG represents
7 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
8 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
9 ordinary skill to seek to reduce TG by the recited amount because there is no significance
10 attached to the amount. Defendants conclude, without support, that there was a reasonable
11 expectation of success without identifying any combination of references and without explaining
12 how each reference relates to the claimed invention.¹³⁴⁰ These contentions: 1) do not assert
13 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
14 analysis; 3) fail to address whether the specific combination of claim elements were all present in
15 the prior art references that would have been combined by a person of ordinary skill in the art to
16 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
17 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
18 element to the point of reading the element out of the claim. Although convenient and expedient,
19 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
20 claim construction, or the law of obviousness.

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22 _____
23 ¹³⁴⁰ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 Defendants do not identify any combination of references and simply provide a laundry
2 list of references that purportedly disclose disparate elements without explaining how they can
3 be combined.¹³⁴¹ As such, Defendants discuss the claim elements in isolation, and fail to address
4 the claimed invention as a whole.¹³⁴² Defendants selectively cite to an unspecified isolated
5 disclosure within a reference without considering other disclosures or even the reference as a
6 whole. Each reference, however, must be evaluated for all that it teaches.¹³⁴³ Defendants’
7 unsupported cobbling of selective disclosures represents hindsight reconstruction.¹³⁴⁴

8 Because Defendants do not identify any combination of references, they necessarily fail
9 to offer any evidence that a person of skill in the art would be motivated to combine those
10 references in order to achieve the invention of the claim as a whole. Defendants make a
11 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
12 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
13 person of ordinary skill to reduce triglycerides by the recited amount.¹³⁴⁵ Defendants’ burden to
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16 ¹³⁴¹ *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”).

17 ¹³⁴² *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”).

18 ¹³⁴³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ¹³⁴⁴ 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”).

20 ¹³⁴⁵ *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

1 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
2 attached to the recited TG reduction amount.¹³⁴⁶ Defendants have not met the burden with the
3 naked assertion that it would have been obvious to seek the claim element.

4 Similarly, without the disclosure of a combination of references and a motivation/reason
5 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
6 person of ordinary skill in the art would have had a reasonable expectation of success in
7 achieving the claimed invention. Defendants make a conclusory statement that there was a
8 reasonable expectation of success, without providing a support other than merely identifying
9 prior art references that purportedly disclose disparate elements.¹³⁴⁷ The mere fact that elements
10 are capable of being physically combined does not establish reasonable expectation of
11 success.¹³⁴⁸

12 (d) Defendants Have Not Shown that Claims 6 and 7 of
13 the ‘715 Patent Would Have Been Obvious

14 Plaintiffs incorporate by reference the discussion related to the independent claims in
15 Section V.B.3. Because Defendants have not shown the obviousness of the independent claims

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18 claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
398, 418 (2007)).

19 ¹³⁴⁶ 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*
20 case of obviousness by establishing that the claimed range is critical”) (internal quotation marks omitted).

21 ¹³⁴⁷ *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).

22 ¹³⁴⁸ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claims 6 and 7.

3 Defendants contend that EPA is known to reduce non-HDL-C and VLDL-C levels.
4 Defendants further contend that a person of ordinary skill would have a reasonable expectation
5 that a composition comprising EPA, but not DHA, would lower non-HDL-C levels, citing a
6 laundry list of references without explaining how each reference relates to the claimed
7 invention.¹³⁴⁹ These contentions: 1) do not assert what the prior art discloses to a person of
8 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
9 specific combination of claim elements were all present in the prior art references that would
10 have been combined by a person of ordinary skill in the art to produce the claimed invention
11 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.
12 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
13 reading the element out of the claim. Although convenient and expedient, Defendants' approach
14 does not conform with the Local Patent Rules of this District, the law of claim construction, or
15 the law of obviousness.

16 Defendants do not identify any combination of references and simply provide a laundry
17 list of references that purportedly disclose disparate elements without explaining how they can
18 be combined.¹³⁵⁰ As such, Defendants discuss the claim elements in isolation, and fail to address
19 the claimed invention as a whole.¹³⁵¹ Defendants selectively cite to an unspecified isolated

20 ¹³⁴⁹ *Id.*

21 ¹³⁵⁰ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

23 ¹³⁵¹ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 disclosure within a reference without considering other disclosures or even the reference as a
2 whole. Each reference, however, must be evaluated for all that it teaches.¹³⁵² Defendants’
3 unsupported cobbling of selective disclosures represents hindsight reconstruction.¹³⁵³

4 Because Defendants do not identify any combination of references, they necessarily fail
5 to offer any evidence that a person of skill in the art would be motivated to combine those
6 references in order to achieve the invention of the claim as a whole. In fact, Defendants do not
7 discuss at all whether a person of ordinary skill would have been motivated to combine the
8 elements.¹³⁵⁴ As such, Defendants fail to demonstrate that there was no motivation to combine
9 the references to achieve the claimed invention.

10 Similarly, without the disclosure of a combination of references and a motivation/reason
11 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
12 person of ordinary skill in the art would have had a reasonable expectation of success in
13 achieving the claimed invention. Defendants make a conclusory statement that a person of
14 ordinary skill “would have a reasonable expectation that a composition comprising EPA, but not
15 DHA would lower non-HDL-C levels,” without providing a support other than simply
16 identifying prior art references that purportedly disclose disparate elements.¹³⁵⁵ The mere fact
17

18 ¹³⁵² *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ¹³⁵³ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
20 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ¹³⁵⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ¹³⁵⁵ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
24 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

1 that elements are capable of being physically combined does not establish reasonable expectation
2 of success.¹³⁵⁶ What is more, Defendants do not even discuss the reasonable expectation of
3 reducing non-HDL-C and VLDL-C levels. As such, Defendants fail to demonstrate reasonable
4 expectation of success of reducing non-HDL-C and VLDL-C levels using the claimed methods.

5 (e) Defendants Have Not Shown that Claim 8 of the
6 '715 Patent Would Have Been Obvious

7 Plaintiffs incorporate by reference the discussion related to the independent claims in
8 Section V.B.3. Because Defendants have not shown the obviousness of the independent claims
9 by clear and convincing evidence, they also have not adequately proven the obviousness of
10 Claim 8.

11 Defendants contend, without support, that the recited reduction in TG represents
12 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to
13 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
14 ordinary skill to seek to reduce TG by the recited amount because there is no significance
15 attached to the amount. Defendants conclude, without support, that there was a reasonable
16 expectation of success without identifying any combination of references and without explaining
17 how each reference relates to the claimed invention.¹³⁵⁷ These contentions: 1) do not assert
18 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious

19 _____
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted).

21 ¹³⁵⁶ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
22 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

23 ¹³⁵⁷ *Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.*

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

8 Defendants do not identify any combination of references and simply provide a laundry
9 list of references that purportedly disclose disparate elements without explaining how they can
10 be combined.¹³⁵⁸ As such, Defendants discuss the claim elements in isolation, and fail to address
11 the claimed invention as a whole.¹³⁵⁹ Defendants selectively cite to an unspecified isolated
12 disclosure within a reference without considering other disclosures or even the reference as a
13 whole. Each reference, however, must be evaluated for all that it teaches.¹³⁶⁰ Defendants’
14 unsupported cobbling of selective disclosures represents hindsight reconstruction.¹³⁶¹

15 Because Defendants do not identify any combination of references, they necessarily fail
16 to offer any evidence that a person of skill in the art would be motivated to combine those
17 references in order to achieve the invention of the claim as a whole. Defendants make a
18

19 ¹³⁵⁸ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

21 ¹³⁵⁹ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ¹³⁶⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹³⁶¹ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
2 reduce triglycerides by 5% to 25%,” without providing a reason that would have prompted a
3 person of ordinary skill to reduce triglycerides by the recited amount.¹³⁶² Defendants’ burden to
4 establish *prima facie* obviousness is not discharged because there is allegedly “no significance”
5 attached to the recited TG reduction amount.¹³⁶³ Defendants have not met the burden with the
6 naked assertion that it would have been obvious to seek the claim element. In addition,
7 Defendants have failed to provide any rationale for the assertion that there would be a reasonable
8 expectation that a composition comprising EPA, but not DHA, would lower non-HDL-C levels.”
9 Defendants provide no explanation for this assertion and instead merely list numerous
10 references.

11 Similarly, without the disclosure of a combination of references and a motivation/reason
12 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
13 person of ordinary skill in the art would have had a reasonable expectation of success in
14 achieving the claimed invention. Defendants make a conclusory statement that there was a
15 reasonable expectation of success, without providing a support other than merely identifying
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18 ¹³⁶² *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
19 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
20 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
21 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
22 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)).

23 ¹³⁶³ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
24 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).

1 prior art references that purportedly disclose disparate elements.¹³⁶⁴ The mere fact that elements
2 are capable of being physically combined does not establish reasonable expectation of
3 success.¹³⁶⁵

4 (f) Defendants Have Not Shown that Claim 9 of the
5 '715 Patent Would Have Been Obvious

6 Plaintiffs incorporate by reference the discussion related to independent claim 1 in
7 Section V.B.3. Because Defendants have not shown the obviousness of Claim 1 by clear and
8 convincing evidence, they also have not adequately proven the obviousness of Claim 9. Claim 9
9 additionally includes the claim element of administering to the subject about 4g of the claimed
10 pharmaceutical composition for a period of 12 weeks to effect a reduction in fasting Lp-PLA2 of
11 at least 15% compared to the second subject.

12 Defendants' contentions fail to disclose each and every element of the claims of the '715
13 patent. Specifically, Defendants do not contend that the relied upon references disclose the
14 following element of Claim 9: *administering 4 g of the composition of the subject daily for a*
15 *period of 12 weeks to effect a reduction in Lp-PLA2 of at least about 15% as compared to the*
16 *Lp-PLA2 level in the second subject.* Therefore, Defendants' prior art combinations cannot
17 render the claims *prima facie* obvious.

18 Defendants contend that "Virani discloses the correlation between Lp-PLA2 and Apo-B,"
19 and that Zalewski discloses that Lp-PL2 co-travels with LDL. Defendants then conclude,
20

21 ¹³⁶⁴ *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be
22 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

23 ¹³⁶⁵ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("[T]he 'predictable
24 result' discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.").

1 without support, that “one of ordinary skill in the art would expect that the claimed methods
2 would reduce Apo-B, discussed above, and would therefore also reduce Lp-PLA2 with a
3 reasonable expectation of success.” Defendants further contend that “given the correlation
4 between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to
5 reduce Lp-PLA2 to therapeutic levels. . . [and] [a]s there is no significance provided by the
6 patentee regarding the various percentage reductions of Lp-PLA2, it would have been obvious”
7 to a person of ordinary skill to seek to reduce Lp-PLA2 by 5% and 15%, with reasonable
8 expectation of success.¹³⁶⁶ These contentions: 1) fail to address whether the specific
9 combination of claim elements were all present in the prior art references that would have been
10 combined by a person of ordinary skill in the art to produce the claimed invention with a
11 reasonable expectation of success; and 2) fail to establish *prima facie* obviousness. Defendants
12 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
13 element out of the claim. Although convenient and expedient, Defendants’ approach does not
14 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
15 obviousness.

16 Virani, Zalewski and Shinozaki do not render Claim 9 obvious. None of the references
17 disclose or suggest the administration of the claimed pharmaceutical compound to effect a
18 reduction in fasting Lp-PLA2 of at least 15%.

19 Virani and Zalewski are both general review articles that discuss Lp-PLA2’s biological
20 role in atherosclerosis. Virani reviews the potential mechanisms by which Lp-PLA2 may
21 “participate in the pathogenesis of atherosclerosis and its clinical manifestations, namely,

22 _____
23 ¹³⁶⁶ Plaintiffs note that Defendants fail to address the specific claim element, which requires a “reduction in fasting
24 Lp-PLA2 of at least 10% compared to the second subject.”

1 coronary artery disease and stroke.”¹³⁶⁷ Zalewski is a highly technical review of the biological
2 role of Lp-PLA2 in atherosclerosis. Neither article suggests or even discusses the administration
3 of any omega-3 fatty acid and any possible effects on Lp-PLA2 that may result. Defendants
4 have failed to identify even a single a prior art reference that discloses the administration of the
5 claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 15%.
6 Defendants fail to provide a basis for their assertion that “one of ordinary skill in the art would
7 expect that the claimed methods would reduce Apo-B, discussed above, and would therefore also
8 reduce Lp-PLA2 with a reasonable expectation of success.” As discussed in Section V.O, a
9 person of ordinary skill in the art did *not* expect that the claimed method would reduce Apo-B.
10 Defendants have failed to prove that a decrease in Apo-B would lead a person of ordinary skill in
11 the art to expect that Lp-PLA2 would also decrease simply because “Lp-PLA2 circulates bound
12 to LDL via Apolipoprotein B.” Defendants have further failed to meet their burden as they do not
13 articulate an “apparent reason” to combine the elements in the manner claimed,¹³⁶⁸ or offer an
14 argument related to “a reasonable expectation of success.”¹³⁶⁹

15 Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and
16 lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Shinozaki
17 does not discuss Lp-PLA2. In fact, Defendants rely on portions of Shinozaki that discuss effects
18 of EPA administration on TG, total cholesterol, and lipoprotein (a) levels. Accordingly,

19 ¹³⁶⁷ Virani at 97.

20 ¹³⁶⁸ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
21 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
22 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

23 ¹³⁶⁹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
24 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

1 Shinozaki does not disclose or suggest the administration of the claimed pharmaceutical
2 compound to effect a reduction in fasting Lp-PLA2 of at least 15%.

3 Defendants do not provide any basis for their assertion that “given the correlation
4 between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to
5 reduce Lp-PLA2 levels to therapeutic levels.” Such an assertion does not provide any evidence
6 of motivation or reasonable expectation of success in achieving the claimed invention, including
7 the reduction in fasting Lp-PLA2 of at least 15%. Further, while Virani discloses that statins and
8 fibrates decrease Lp-PLA2, there is no mention of the use of omega-3 fatty acids.¹³⁷⁰ Virani and
9 Zalewski disclose that further research needs to be conducted regarding the relationship between
10 Lp-PLA2 and atherosclerosis.¹³⁷¹

11 Defendants fail to provide any factual basis to support their allegation of obviousness and
12 reasonable expectation of success. Accordingly claim 9 of the '715 Patent is not obvious in light
13 of Virani, Zalewski and/or Shinozaki.

14 (g) Defendants Have Not Shown that Claim 10 of the
15 '715 Patent Would Have Been Obvious

16 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
17 Section V.B.3. Because Defendants have not shown the obviousness of the Independent Claims
18 by clear and convincing evidence, they also have not adequately proven the obviousness of
19 Claim 10.
20

21
22 ¹³⁷⁰ Virani at 101.

23 ¹³⁷¹ Virani at 101 (“Understanding the role of Lp-PLA2 provides further insights into the process of atherosclerosis
24 and vascular inflammation.”); Zalewski at 928 (“To this end, future mechanistic studies need to address whether this
approach abrogates inflammation in atherosclerotic tissue and produces favorable changes in intermediate
cardiovascular end points.”).

1 Defendants contend, without support, that a person of ordinary skill would naturally seek
2 to reduce total cholesterol level because it represents therapeutic efficacy. Defendants further
3 contend that recited percentage reductions of total cholesterol are obvious because there is no
4 significance regarding the percentage reductions. Defendants conclude, without support, that
5 there was a reasonable expectation of success without identifying any combination of references
6 and without explaining how each reference relates to the claimed invention. These contentions:
7 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are
8 irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim
9 elements were all present in the prior art references that would have been combined by a person
10 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of
11 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
12 analysis, but trivialize the claim element to the point of reading the element out of the claim.
13 Although convenient and expedient, Defendants' approach does not conform with the Local
14 Patent Rules of this District, the law of claim construction, or the law of obviousness.

15 Defendants do not identify any combination of references and simply provide a laundry
16 list of references that purportedly disclose disparate elements without explaining how they can
17 be combined.¹³⁷² As such, Defendants discuss the claim elements in isolation, and fail to address
18 the claimed invention as a whole.¹³⁷³ Defendants selectively cite to an unspecified isolated
19 disclosure within a reference without considering other disclosures or even the reference as a
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21 ¹³⁷² *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

23 ¹³⁷³ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 whole. Each reference, however, must be evaluated for all that it teaches.¹³⁷⁴ Defendants’
2 unsupported cobbling of selective disclosures represents hindsight reconstruction.¹³⁷⁵

3 Because Defendants do not identify any combination of references, they necessarily fail
4 to offer any evidence that a person of skill in the art would be motivated to combine those
5 references in order to achieve the invention of the claim as a whole. Defendants make a
6 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
7 reduce total cholesterol by 5% to 15%,” without providing a reason that would have prompted a
8 person of ordinary skill to reduce total cholesterol by the recited amount.¹³⁷⁶ Defendants’ burden
9 to establish *prima facie* obviousness is not discharged because there is allegedly “no
10 significance” attached to the recited total cholesterol reduction amount.¹³⁷⁷ Defendants have not
11 met the burden with the naked assertion that it would have been obvious to seek the claimed
12 element.

13 Similarly, without the disclosure of a combination of references and a motivation/reason
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
15 person of ordinary skill in the art would have had a reasonable expectation of success in
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17 _____
¹³⁷⁴ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

18 ¹³⁷⁵ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
19 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

20 ¹³⁷⁶ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
22 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ¹³⁷⁷ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
24 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).

1 achieving the claimed invention. Defendants make a conclusory statement that there was a
2 reasonable expectation of success, without providing a support other than merely identifying
3 prior art references that purportedly disclose disparate elements.¹³⁷⁸ The mere fact that elements
4 are capable of being physically combined does not establish reasonable expectation of
5 success.¹³⁷⁹

6 (h) Defendants Have Not Shown that Claim 14 of the
7 ‘715 Patent Would Have Been Obvious

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

12 Defendants’ contentions fail to disclose each and every element of the claim 14 of the
13 ‘715 patent. Specifically, Defendants do not contend that the relied upon references disclose the
14 following elements of Claim 14: (1) administering the claimed pharmaceutical composition to
15 the recited subject to effect a statistically significant reduction in triglycerides *and*
16 *Apolipoprotein B* without effecting a statistically significant increase in LDL-C in the subject.
17 Therefore, Defendants’ prior art combinations cannot render the claims *prima facie* obvious.

18 Defendants contend, without support, that the recited reduction in TG represents
19 therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to

20 ¹³⁷⁸ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
22 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

23 ¹³⁷⁹ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

1 therapeutic efficacy. Defendants further contend that it would have been obvious to a person of
2 ordinary skill to seek to reduce TG by the recited amount because there is no significance
3 attached to the amount. Defendants conclude, without support, that there was a reasonable
4 expectation of success without identifying any combination of references and without explaining
5 how each reference relates to the claimed invention.¹³⁸⁰ These contentions: 1) do not assert
6 what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious
7 analysis; 3) fail to address whether the specific combination of claim elements were all present in
8 the prior art references that would have been combined by a person of ordinary skill in the art to
9 produce the claimed invention with a reasonable expectation of success; and 4) fail to establish
10 *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim
11 element to the point of reading the element out of the claim. Although convenient and expedient,
12 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
13 claim construction, or the law of obviousness.

14 Defendants do not identify any combination of references or any references that disclose
15 any of the claim elements.¹³⁸¹ Because Defendants do not identify any combination of
16 references, they necessarily fail to offer any evidence that a person of skill in the art would be
17 motivated to combine those references in order to achieve the invention of the claim as a whole.
18 Defendants make a conclusory statement that "it would have been obvious to the ordinarily
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20 ¹³⁸⁰ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
21 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
22 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

23 ¹³⁸¹ *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
24 demonstrating that each of its elements was, independently, known in the prior art").

1 skilled artisan to seek to reduce triglycerides by, for example, 25% without increasing LDL-C by
2 more than 5%,” without providing a reason that would have prompted a person of ordinary skill
3 to reduce triglycerides by the recited amount.¹³⁸² Defendants fail to provide any argument
4 related to motivation to effect a statistically significant reduction in Apo-B, as required by the
5 claim. Defendants’ burden to establish *prima facie* obviousness is not discharged because there
6 is allegedly “no significance” attached to the recited TG reduction amount.¹³⁸³ Defendants have
7 not met the burden with the naked assertion that it would have been obvious to seek the claim
8 element.

9 Similarly, without the disclosure of a combination of references and a motivation/reason
10 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
11 person of ordinary skill in the art would have had a reasonable expectation of success in
12 achieving the claimed invention. Defendants make a conclusory statement that there was a
13 reasonable expectation of success, without providing any support.¹³⁸⁴ Defendants fail to provide
14 any statement related to reasonable expectation of success of effecting a statistically significant
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16 ¹³⁸² *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
17 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
18 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
19 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350,
20 1356-57 (Fed. Cir. 2007) (“While the *KSR* Court rejected a rigid application of the teaching, suggestion, or
21 motivation (‘TSM’) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason
22 that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the
23 claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S.
24 398, 418 (2007)).

¹³⁸³ 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).

¹³⁸⁴ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

1 reduction in Apo-B, as required by the claim. As such, Defendants fail to demonstrate
2 reasonable expectation of success of the claimed invention.

3 (i) Defendants Have Not Shown that Claims, 11, 15,
4 and 18 of the '715 Patent Would Have Been
Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
6 Section V.B.3. Because Defendants have not shown the obviousness of the Independent Claim
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 11, 15, and 17.

9 Defendants contend that it would be obvious to use the claimed methods to treat patients
10 who consume a Western diet, because cardiovascular disease is a leading cause of death in the
11 United States and most European countries, and because it was common practice to advise
12 patients receiving triglyceride-lowering treatments to maintain their diet. These contentions: 1)
13 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant
14 to an obvious analysis; 3) fail to address whether the specific combination of claim elements
15 were all present in the prior art references that would have been combined by a person of
16 ordinary skill in the art to produce the claimed invention with a reasonable expectation of
17 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
18 analysis, but trivialize the claim element to the point of reading the element out of the claim.
19 Although convenient and expedient, Defendants' approach does not conform with the Local
20 Patent Rules of this District, the law of claim construction, or the law of obviousness.

21 Defendants do not identify any combination of references and simply provide a list of
22 references that purportedly disclose disparate elements without explaining how they can be
23
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1 combined.¹³⁸⁵ Defendants offer no support or explanation for their assertion that “it is a well-
2 known, common practice to advise patients receiving triglyceride-lowering treatments to
3 maintain their diet.” As an initial matter, Defendants’ assertion—even if true—does not support
4 their obviousness claim and Defendants do not explain the connection between “maintain[ing]”
5 diet and the asserted claim. Defendants offer a laundry list of citations that do not appear to
6 support their unexplained assertion. Further, Defendants discuss the claim elements in isolation,
7 and fail to address the claimed invention as a whole.¹³⁸⁶ Defendants selectively cite to an
8 unspecified isolated disclosure within a reference without considering other disclosures or even
9 the reference as a whole. Each reference, however, must be evaluated for all that it teaches.¹³⁸⁷
10 Defendants’ unsupported cobbling of selective disclosures represents hindsight
11 reconstruction.¹³⁸⁸

12 Because Defendants do not identify any combination of references, they necessarily fail
13 to offer any evidence that a person of skill in the art would be motivated to combine those
14 references in order to achieve the invention of the claim as a whole. Defendants merely state that
15 the cardiovascular disease is a leading cause of death in the United States and most European
16
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19 ¹³⁸⁵ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

21 ¹³⁸⁶ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ¹³⁸⁷ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹³⁸⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 countries, and do not explain how that would have prompted a person of ordinary skill to use the
2 claimed method to treat patients who consume a Western diet.¹³⁸⁹

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. In fact, other than simply identifying prior art references that
7 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
8 ordinary skill would have expected that the combination to work for its intended purpose.¹³⁹⁰ As
9 such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

10 4. The '715 Patent is Not Invalid Under § 112

11 a) Defendants Have Not Demonstrated that the Claims of the '715 12 Patent Are Invalid for Indefiniteness

13 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
14 the subject matter which the applicant regards as his invention.”¹³⁹¹ Patent claims are valid in
15 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
16

17 ¹³⁸⁹ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
19 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
20 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
21 determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

22 ¹³⁹⁰ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
23 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
24 combined, but also that the combination would have worked for its intended purpose.”)

¹³⁹¹ 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.

1 art about the scope of the invention” in light of the specification and the prosecution history.¹³⁹²

2 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
3 and “the certainty which the law requires in patents is not greater than is reasonable.”¹³⁹³

4 Defendants allege that a number of terms containing the phrases “about” and
5 “substantially” are indefinite. Defendants do not provide any reason why these terms are
6 indefinite other than that they contain the phrases “about,” “substantially,” and “statistically
7 significant.” But, of course, these terms are routinely used in patent claims, and are not *per se*
8 indefinite.¹³⁹⁴ In particular, courts have held repeatedly that claims that contain the words
9 “about” and “substantially” are not indefinite.¹³⁹⁵ Here, a person of ordinary skill would
10 understand with reasonable certainty what is claimed when the claims are read in light of the
11 specification and prosecution history.¹³⁹⁶ Therefore, the terms that contain the words “about,”
12 “substantially,” and “statistically significant” are not invalid for being indefinite.

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14 ¹³⁹² *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

15 ¹³⁹³ *Id.* at 2129.

16 ¹³⁹⁴ *Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1370 (Fed. Cir. 2014) (“Claim language employing terms
17 of degree has long been found definite where it provided enough certainty to one of skill in the art when read in the
18 context of the invention.”); *see also BJ Servs. Co. v. Halliburton Energy Servs., Inc.*, 338 F.3d 1368, 1372 (Fed. Cir.
19 2003) (“The question becomes whether one of ordinary skill in the art would understand what is claimed when the
20 claim is read in light of the specification.”) (discussing the term “about”); *Verve, LLC v. Crane Cams, Inc.*, 311 F.3d
21 1116, 1120 (Fed. Cir. 2002) (“It is well established that when the term ‘substantially’ serves reasonably to describe
22 the subject matter so that its scope would be understood by persons in the field of the invention, and to distinguish
23 the claimed subject matter from the prior art, it is not indefinite.”).

20 ¹³⁹⁵ *See, e.g., Deere & Co. v. Bush Hog, LLC*, 703 F.3d 1349, 1359 (Fed. Cir. 2012) (rejecting contention that claim
21 term “substantially planar” is indefinite); *Enzo Biochem, Inc. v. Applera Corp.*, 599 F.3d 1325, 1335 (. 2010)
22 (holding that the claim phrase “not interfering substantially” was not indefinite even though the construction
23 “define[d] the term without reference to a precise numerical measurement”); *BJ Services Co. v. Halliburton Energy
24 Services, Inc.*, 338 F.3d 1368, 1372–73 (Fed. Cir. 2003) (affirming jury’s verdict that claims reciting a concentration
as “about 0.06” were not invalid for being indefinite); *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540,
1557 (Fed. Cir. 1983) (ruling that the claim term “stretching ... at a rate exceeding about 10% per second” is not
indefinite).

23 ¹³⁹⁶ *See generally* the ’715 patent and its prosecution history.

1 Defendants further allege that the terms “a pharmaceutical composition comprising at
2 least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” and “wherein no
3 fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about
4 0.6% by weight of all fatty acids combined” are indefinite. They contend that, because there is
5 no indication of how much of the pharmaceutical composition is composed of fatty acids, by
6 extension it is indefinite how much of each fatty acid is present in the composition. This is
7 incorrect. A claim can use a ratio to define amounts of components in a product, using terms
8 such as “percent by weight.”¹³⁹⁷ In light of the specification and prosecution history, a person of
9 ordinary skill would understand with reasonable certainty the range of relative quantities of EPA,
10 DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty
11 acids present.¹³⁹⁸ Therefore, these terms are not indefinite and do not render the claims
12 indefinite.

13 Defendants further allege that the term “who does not receive concurrent lipid altering
14 therapy” is indefinite. Defendants provide no basis for this allegation. In light of the
15 specification and the prosecution history, however, a person of ordinary skill in the art would
16 understand with reasonable certainty the scope of a “concurrent lipid altering therapy.”¹³⁹⁹
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20 ¹³⁹⁷ *T.F.H. Publications, Inc. v. Dorskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J.
21 Mar. 5, 2012) (construing “by weight” to mean the weight of a first component was in a ratio to the weight of a
22 second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27,
2011) (construing percent by weight to mean “ratio of the weight of the ingredient in question divided by the total
volume of the solution, with this ratio expressed as a percentage”).

23 ¹³⁹⁸ See generally the ’728 patent and its prosecution history.

24 ¹³⁹⁹ See generally the ’715 patent and its prosecution history.

1 Moreover, lipid altering therapies are discussed in the patent specification.¹⁴⁰⁰ Therefore, the
2 phrase “concurrent lipid altering therapy” does not render the claim indefinite.

3 Defendants further allege that the term “consume a Western diet” is indefinite because it
4 is “too vague.” But the specification and the prosecution history describe (and even define) a
5 “Western diet.”¹⁴⁰¹ In light of the specification and the prosecution history, a person of ordinary
6 skill would know with reasonable certainty the scope of the term “Western diet” and therefore
7 does not render the claims indefinite.

8 Defendants also allege that it is impossible to ascertain the metes and bounds of
9 “compared to . . . a second subject having a fasting baseline triglyceride level of 500 mg/dl to
10 about 1500 mg/dl . . .” A person of ordinary skill, however, would understand the metes and
11 bounds of the term in light of the specification and the prosecution history.¹⁴⁰² Moreover, the
12 method of comparing a subject to a second subject, such as a placebo controlled, randomized,
13 double blind study, would have been known to a person of ordinary skill at the time of the
14 invention. Therefore, the term does not render the claims indefinite.

15 Defendants further contend that the metes and bounds of the phrase “a statistically
16 significant reduction in triglycerides without effecting a statistically significant increase in LDL-
17 C or Apolipoprotein B in the subject” is unclear. Defendants do not provide the basis for the
18 assertion other than stating that it is unclear and the specification does not clarify its meaning.
19 As discussed above, use of the phrase “statistically significant” does not render a claim *per se*
20 indefinite. In light of the specification and the prosecution history, a person of ordinary skill in
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22 ¹⁴⁰⁰ See e.g., ‘715 patent at 12:43-46; 13:66-14:5.

23 ¹⁴⁰¹ See generally the ‘715 patent and its prosecution history.

24 ¹⁴⁰² See generally the ‘715 patent and its prosecution history.

1 the art would know with reasonable certainty the scope of the term “a statistically significant
2 reduction in triglycerides without effecting a statistically significant increase in LDL-C or
3 Apolipoprotein B in the subject” and therefore does not render the claims indefinite.¹⁴⁰³

4 Finally, Defendants contend that the asserted claims improperly mix methods and
5 formulations because Plaintiffs’ assertion of contributory infringement apparently suggests that
6 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
7 analysis is based on what the claim language informs a person of ordinary skill in the art in light
8 of the specification and the prosecution history. Defendants do not identify any actual claim
9 language that mixes methods and formulations. Moreover, contributory infringement may be
10 asserted and proven when a party sells “a material or apparatus for use in *practicing a patented*
11 *process . . . knowing the same to be especially made or especially adapted for use in an*
12 *infringement of such patent.*”¹⁴⁰⁴ Plaintiffs assert that Defendants’ ANDA products will be used
13 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
14 itself directly infringes. Therefore, Defendants’ interpretations of Plaintiffs’ assertions are
15 mistaken and the ’715 patent claims are not indefinite for improperly mixing methods and
16 formulations.

17 Defendants argue that it is not clear who “the second subject” in Claim 18 is or why they
18 must consume a Western diet. A person of ordinary skill in the art would understand that Claim
19 18 discloses a “The method of Claim 17 wherein the subject consumes a Western diet.” This
20 interpretation is not subject to reasonable debate based on consideration of the claim language
21 and the specification and the prosecution history does not suggest a different interpretation of the
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23 ¹⁴⁰³ See generally the ’715 patent and its prosecution history.

24 ¹⁴⁰⁴ 35 U.S.C. § 271(c) (emphasis added).

1 claims. Also, the district court can retroactively correct certain errors in a patent’s claims if “(1)
2 the correction is not subject to reasonable debate based on consideration of the claim language
3 and the specification and (2) the prosecution history does not suggest a different interpretation of
4 the claims.”¹⁴⁰⁵ In this case, any correction would be directed to an element that is not subject to
5 reasonable debate and the prosecution history and specification do not suggest a contrary
6 interpretation.

7 b) Defendants Have Not Demonstrated that the Claims of the ‘715
8 Patent Are Invalid for Insufficient Written Description

9 The first paragraph of 35 U.S.C. § 112 requires that a patent specification “contain a
10 written description of the invention.” This requires that the specification “reasonably convey”
11 that the applicant “invented” or “had possession” of the claimed subject matter when the
12 application was filed.¹⁴⁰⁶ Support need not be literal¹⁴⁰⁷—it may be implicit¹⁴⁰⁸ or inherent¹⁴⁰⁹ in
13 the disclosure. In addition, it is unnecessary to include information that is already known or
14 available to persons of ordinary skill.¹⁴¹⁰

15 Defendants make three arguments regarding the written description requirement. First,
16 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack

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18 ¹⁴⁰⁵ *Novo Indus., L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354, 1357 (Fed. Cir. 2003). These “determinations
19 must be made from the point of view of one skilled in the art.” *Ultimax Cement Mfg. v. CTS Cement Mfg.*, 587 F.3d
20 1339, 1353 (Fed. Cir. 2009).

21 ¹⁴⁰⁶ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

22 ¹⁴⁰⁷ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
23 422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

24 ¹⁴⁰⁸ *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.

¹⁴⁰⁹ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

¹⁴¹⁰ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

1 written description. This is incorrect. The specification of asserted patents literally discloses the
2 claimed invention.¹⁴¹¹ Moreover, the recited baseline TG levels of the claimed invention appear
3 in the original claims of the application to which the asserted patent claims priority. Thus, there
4 is a strong presumption that the claimed invention is adequately described.¹⁴¹² Defendants do
5 not and cannot rebut this presumption. Specifically, the patient population is originally claimed
6 as “a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500
7 mg/dl.”¹⁴¹³ The asserted claims recite the same patient population. Defendants do not contend
8 that the patient population of the asserted claims is not literally described by the specification
9 and in the original claims of the application to which the asserted patent claims priority. In fact,
10 the specification and the provisional patent application claims at the time of filing describe these
11 limitations.¹⁴¹⁴ Therefore, Defendants have failed to explain whether and how an aspect of the
12 claimed invention has not been described with sufficient particularity such that one skilled in the
13 art would recognize that the applicant had possession of the claimed invention.

14 Second, Defendants contend that “a person of skill in the art would not understand that
15 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
16 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
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19 ¹⁴¹¹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
20 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
legal foundation for claiming that species.”).

21 ¹⁴¹² *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
22 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

23 ¹⁴¹³ See U.S. Application No. 12/702,889.

24 ¹⁴¹⁴ See e.g., ‘715 patent at 13:29-34; 14:49-51; U.S. Application No. 12/702,889.

1 dosages and quantities of the claimed methods.¹⁴¹⁵ Moreover, the dosages and quantities of the
2 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
3 claimed invention is adequately described.¹⁴¹⁶ Defendants do not and cannot rebut this
4 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
5 to about 4g.”¹⁴¹⁷ The asserted claims recite “4 g.” Defendants do not contend that dosages and
6 quantities of the asserted claims are not literally described by the specification and in the original
7 claims. In fact, the specification and the provisional patent application claims, at the time of
8 filing, described these limitations. Therefore, Defendants have failed to explain whether and
9 how an aspect of the claimed invention has not been described with sufficient particularity such
10 that one skilled in the art would recognize that the applicant had possession of the claimed
11 invention.

12 Third, Defendants contend that “a person of skill in the art would not understand that the
13 inventor was in possession of a method comprising a comparison against a second subject or
14 against a second population.” The specification demonstrates that the applicants were in
15 possession of the claimed inventions. For example, a person of ordinary skill would have
16 understood that the inventor was in possession of a method comprising administration of a
17 composition with the recited properties, based on a comparison of a subject or a population
18 against a second subject or a second population.

20 ¹⁴¹⁵ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

23 ¹⁴¹⁶ *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

¹⁴¹⁷ See U.S. Application No. 12/702,889.

1 Fourth, Defendants contend that “nowhere does the specification of the ‘715 patent
2 describe or suggest comparing the effects of administering a composition in a subject against a
3 second subject.” The specification demonstrates that the inventors were in possession of a
4 method of treating a patient with the claimed composition and having the claimed effects.
5 Indeed, the claim limitations are stated in the specification. Moreover, an example with a
6 clinical study protocol is disclosed.

7 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,¹⁴¹⁸ the court
8 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
9 specification of asserted patents literally disclose the claimed invention in the specification and
10 the claims as originally filed. Thus, an examination of the four corners of the specification from
11 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
12 asserted patents were in possession of the claimed invention.

13 Defendants conclude by alleging that the specification does not describe anything more
14 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
15 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
16 specification; nonobviousness can be supported by post-filing date evidence for example.¹⁴¹⁹
17 Written description requires only that the specification reasonably conveys that the applicant had
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20 ¹⁴¹⁸ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

21 ¹⁴¹⁹ See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
22 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
23 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
24 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
1307 (. 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 (. 2004) (“Evidence
developed after the patent grant is not excluded from consideration, for understanding of the full range of an
invention is not always achieved at the time of filing the patent application.”).

1 possession of the claimed subject matter when the application was filed. Therefore, whether the
2 claims are obvious has no bearing on the adequacy of written description.

3 c) Defendants Have Not Demonstrated that the Claims of the ‘715
4 Patent Are Invalid for Lack of Enablement

5 The first paragraph of 35 U.S.C. § 112 requires that the specification “enable any person
6 skilled in the art . . . to make and use [the claimed invention].” A claim is not enabled if it would
7 require undue experimentation for a person of ordinary skill to make or use the invention.
8 Factors that may be considered include the quantity of experimentation necessary, the amount of
9 direction or guidance presented, the presence or absence of working examples, the nature of the
10 invention, the state of the prior art, the relative skill of those in the art, the predictability or
11 unpredictability of the art, and the breadth of the claims.¹⁴²⁰ The enablement requirement is
12 separate and distinct from the written description requirement,¹⁴²¹ and as such a claim does not
13 require descriptive support in the disclosure as originally filed for it to be enabled.¹⁴²²

14 Defendants make three specific arguments regarding the enablement requirement. First,
15 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
16 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
17 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
18 skill would be able to determine the amounts of the components in the pharmaceutical
19 composition without any experimentation, much less undue experimentation.

20 Second, Defendants contend that it would take undue experimentation to obtain the
21 claimed required results listed in the full scope of the patent claims, including the claimed lipid

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¹⁴²⁰ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ¹⁴²¹ *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ¹⁴²² MPEP § 2164.

1 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
2 method and certainly not undue experimentation. Administration of a recited amount of a recited
3 composition, for a recited duration, to a specific, recited patient population produces the recited
4 results. No additional experimentation is required, and Defendants do not explain their
5 allegation that undue experimentation would be required. Defendants also do not contend that
6 following the claimed method (each recited element) does not produce the recited results. The
7 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
8 demonstrate that administration of EPA of the recited composition, when administered to
9 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
10 results.¹⁴²³ Therefore, the claims are not invalid for lack of enablement.

11 Third, Defendants allege that “it would require undue experimentation to obtain the
12 claimed required results in subjects who do ‘not receive concurrent lipid altering therapy’
13 because the patentee did not separately study such subjects.” Yet, as Defendants admit, the
14 example in the specification includes both subjects who did not receive concurrent lipid altering
15 therapy. This is consistent with the prosecution history, which includes a study of both subjects
16 on statins and not on statins.

17 Defendants conclude by alleging that the specification does not enable anything more
18 than what is obvious over the prior art or was known to a person of skill in the art. First,
19 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
20 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
21 precluded in the future from raising any new legal theory to support this assertion. Moreover,
22 while the ’715 patent’s specification enables a person of ordinary skill to obtain the claimed
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24 ¹⁴²³ See VASCEPA Prescribing Information at Table 2.

1 limitations without undue experimentation, the claimed limitations would not have been obvious to a
2 person of ordinary skill, as discussed in Section V.B.3. Furthermore, Plaintiffs have initiated
3 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
4 claimed methods.^{1424, 1425} Therefore, a person of ordinary skill would have concluded that the
5 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

6 **C. The '335 Patent**

7 **1. The '335 Patent Claims Eligible Subject Matter Under § 101**

8 Defendants' allegation that the asserted claims of the '335 patent relate to ineligible
9 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
10 case under Section 101 or provide a legal or factual basis to support their allegations.

11 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local
12 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
13 provided.¹⁴²⁶ The bare assertion of invalidity under Section 101 without providing the grounds
14 for such an allegation and examining the elements of the asserted claims of the '335 patent does
15 not meet this requirement and thwarts the purpose of the Rules.¹⁴²⁷

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18 ¹⁴²⁴ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any
19 doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical
20 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
21 the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.").

22 ¹⁴²⁵ See May 16, 2011 Bays Declaration at Appendix B.

23 ¹⁴²⁶ See Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all
24 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
statement of any grounds of invalidity based on 35 U.S.C. § 101.").

¹⁴²⁷ Nor does the preceding paragraph, which provides only a purported summary of the claims of the '335 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

1 The inquiry under Section 101 involves a two-step test: first, a court must determine
2 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
3 phenomenon, or abstract idea.¹⁴²⁸ Second, even if the claim is directed to one of these concepts,
4 it still may be patent eligible and the court must determine what else is part of the claim.¹⁴²⁹

5 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
6 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
7 the '335 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
8 conventional” steps, and the only novel element related to administering the proper dosage based
9 on a natural law observation.¹⁴³⁰ However, the claims merely recited this natural law without
10 reciting any novel application of it.¹⁴³¹ The Court found that providing protection to such
11 claims would result in pre-empting “a broad range of potential uses” and excluding others from
12 using “the basic tools of scientific and technical work.”¹⁴³² A method of treatment claim,
13 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
14 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
15 protection.¹⁴³³

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18 early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
19 contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

18 ¹⁴²⁸ *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
19 issue are directed to one of those patent-ineligible concepts.”).

20 ¹⁴²⁹ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, “[w]hat else is there in the claims before us?”).

21 ¹⁴³⁰ *Mayo*, 132 S. Ct. at 1294.

22 ¹⁴³¹ *Id.* at 1301.

23 ¹⁴³² *Id.*

24 ¹⁴³³ *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

1 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
2 occurring substance. It is not. Even references contained within Defendants’ own contentions
3 make clear that EPA of the requisite purity and characteristics is not found in nature.¹⁴³⁴ As
4 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
5 decades it has been accepted that compositions isolated from nature or purified beyond their
6 natural state are patent-eligible.¹⁴³⁵ Moreover, Defendants’ assertions are immaterial to a Section
7 101 defense because method of treatment claims like the ones asserted in this case are patent
8 eligible even if they are directed to administration of a naturally occurring substance.¹⁴³⁶

9 To the extent Defendants are arguing that a law of nature both underlies the claims and
10 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
11 claimed effects are the natural result of ingesting a naturally-occurring substance.”¹⁴³⁷ Since the
12 composition that is the subject of the claims is not naturally occurring, Defendants appear to
13 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
14 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
15 characterization of laws of nature.¹⁴³⁸ To say that the claims of the ’335 patent claim a law of
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17 1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
18 eligible claims, such as method of treatment claims, would also be necessarily ineligible).

19 ¹⁴³⁴ See, e.g., U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
20 Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidation Contentions, e.g., at 26–27).

21 ¹⁴³⁵ 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
22 (CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

23 ¹⁴³⁶ *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

24 ¹⁴³⁷ See Defendants’ Joint Invalidation Contentions at 473.

¹⁴³⁸ 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

1 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
2 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
3 underlying principles of nature” that would “make all inventions unpatentable.”¹⁴³⁹ Indeed, even
4 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
5 claims not treatment claims of the type that *Mayo* stated were typical and patentable.¹⁴⁴⁰

6 Even if there is some underlying law of nature in the asserted claims, the subject matter
7 of the '335 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
8 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
9 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
10 foreclose from others the use of that equation in conjunction with all of the other steps in their
11 claimed process.’”¹⁴⁴¹ As discussed above, the asserted claims of the '335 patent contain a
12 novel, unconventional, and specific method of treatment comprising a particularized application
13 of a nonnaturally occurring substance and does not preempt the use of a law of nature.¹⁴⁴²

14 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
15 arguments are further evidence of invalidity under § 101. This argument is without merit. The
16 claims are enabled and written description is satisfied for the reasons discussed below. In
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19 to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
20 aspirin).”).

21 ¹⁴³⁹ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

22 ¹⁴⁴⁰ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
23 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
24 particularly in the area of diagnostic research.”).

¹⁴⁴¹ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

¹⁴⁴² 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).

1 addition, as discussed above, the asserted claims are not merely a naturally-occurring
2 phenomena, and thus satisfy the requirements of § 101.¹⁴⁴³

3 **2. The Asserted Claims of the ‘335 Patent Are Not Anticipated by WO**
4 **‘118**

5 To anticipate, a single prior art reference must sufficiently describe a claimed invention
6 so that the public is in “possession” of that invention.¹⁴⁴⁴ Therefore, to anticipate, a reference
7 must set forth every element of the claim, either expressly or inherently, in as complete detail as
8 is contained in the claim.¹⁴⁴⁵ The claim elements must also be “arranged” in the prior art
9 reference, just as they are in the claim,¹⁴⁴⁶ rather than as “multiple, distinct teachings that the
10 artisan might somehow combine to achieve the claimed invention.”¹⁴⁴⁷ In addition, public
11 “possession” requires that the prior art enable a person of ordinary skill to make and use the
12 invention without undue experimentation.¹⁴⁴⁸ Factors that may be included in this analysis
13 include the quantity of experimentation necessary, the amount of direction or guidance
14 presented, the presence or absence of working examples, the nature of the invention, the state of
15 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,

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17
18 ¹⁴⁴³ See, e.g., *Oleksy v. Gen. Elec. Co.*, 2013 WL 3233259, at *5 (N.D. Ill. June 26, 2013) (rejecting a challenge
under *Mayo* because the patent claim “contains specifically defined, non-conventional steps” and is “is limited to [a]
particular application.”).

19 ¹⁴⁴⁴ *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

20 ¹⁴⁴⁵ *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).

21 ¹⁴⁴⁶ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

22 ¹⁴⁴⁷ *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).

23 ¹⁴⁴⁸ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,*
Inc. v. Ivax Pharms., Inc., 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

1 and the breadth of the claims.¹⁴⁴⁹ This inquiry is objective, and thus evidence of undue
2 experimentation need not be prior art.¹⁴⁵⁰

3 Defendants assert that Claims 1-29 of the '335 Patent are anticipated by the WO '118
4 reference.¹⁴⁵¹

5 A element-by-element analysis, identifying each element of each asserted claim that is
6 absent from WO '118, is provided below. The contentions below are incorporated by reference
7 into Exhibit C, and vice-versa. WO '118 does not anticipate the claims of the '335 patent
8 because it does not describe, properly arrange, or enable the '335 patent claims.

9 a) WO '118 Does Not Teach Every Element of the Claims of the
10 '335 Patent

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

12 It is well established that, for a prior art reference to anticipate, “every element of the
13 claimed invention must be identically shown in a single reference.”¹⁴⁵² Moreover, the elements
14 of the claimed invention must have “strict identity” with the elements of the reference; “minimal
15 and obvious” differences are sufficient to prevent anticipation.¹⁴⁵³ Here, WO '118 entirely fails
16 to disclose the following elements of Claim 1 of the '335 Patent: *effective to reduce fasting*
17 *triglycerides by at least about 15% compared to a fasting triglyceride level at a baseline prior to*

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19 ¹⁴⁴⁹ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

20 ¹⁴⁵⁰ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999
21 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

22 ¹⁴⁵¹ 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.

23 ¹⁴⁵² *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).

24 ¹⁴⁵³ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 *initial administration of the pharmaceutical composition.* WO '118 further entirely fails to
2 disclose the following elements of Claim 14 of the '335 Patent: *effective to reduce fasting*
3 *triglycerides by at least 25% and to reduce fasting Apolipoprotein B, compared to a second*
4 *subject having a baseline triglyceride level of 500 mg/dl to about 2000 mg/dl who has not*
5 *received the pharmaceutical composition and is not on concomitant statin therapy.* WO '118
6 also entirely fails to disclose the following elements of Claim 22 of the '335 Patent: *the subject*
7 *exhibits a reduction in fasting triglycerides of at least about 25% and a reduction in fasting*
8 *Apolipoprotein B compared to a control subject having a baseline triglyceride level of 500 mg/dl*
9 *to about 2000 mg/dl who has not received the pharmaceutical composition and is not on*
10 *concomitant lipid altering therapy.* Defendants appear to concede that WO '118 does not
11 expressly teach these elements, as they fail to set forth any basis for concluding that WO '118
12 teaches this element.¹⁴⁵⁴ Indeed, Defendants could not set forth any basis for concluding that
13 WO '118 teaches this element because WO '118 does not.

14 Instead, Defendants argue that these elements express the intended result of a method that
15 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
16 below, WO '118 fails to disclose each element of the independent claims of the '335 Patent,
17 either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method.
18 Defendants also argue that these elements represent inherent, natural properties of EPA, and are
19 entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of
20 anticipation and claim construction. Further, while Defendants argue that the inherent properties
21 are exemplified in the prior art, they fail to identify even a single prior art reference that makes
22 such a disclosure. Defendants cannot point to a single, specific prior art reference because the

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24 ¹⁴⁵⁴ Defendants' Invalidity Contentions at 202-204.

1 | claimed pharmaceutical composition has never been administered in the manner claimed to the
2 | claimed patient population. Also, these elements are positively recited in the body of the claim
3 | and therefore cannot be construed as a non-limiting preamble and must be given patentable
4 | weight.

5 | Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
6 | effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
7 | inherently anticipate as a matter of law.”¹⁴⁵⁵ “[A]nticipation by inherent disclosure is appropriate
8 | only when the reference discloses prior art that must *necessarily* include the unstated
9 | limitation.”¹⁴⁵⁶ “It is not sufficient if a material element or limitation is ‘merely probably or
10 | possibly present’ in the prior art.”¹⁴⁵⁷ WO ‘118 fails to provide any data related to the lipid
11 | effects of the disclosed invention on patients described in the publication. Therefore, Defendants
12 | fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets
13 | the elements of the independent claims every time it is administered.

14 | Defendants fail to demonstrate that administration of the claimed EPA compositions
15 | “*necessarily*” yields the claimed lipid effects. For example, one study cited by Defendants
16 | suggests that EPA administration may increase LDL-C.¹⁴⁵⁸ Rambjor is a clinical study which
17 | administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
18 | and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
19 | non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
20 | decrease TG without increasing LDL-C *every time it is administered*.

21 | _____
22 | ¹⁴⁵⁵ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 | ¹⁴⁵⁶ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 | ¹⁴⁵⁷ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

¹⁴⁵⁸ *See, e.g., Rambjor*.

1 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
2 properly construed as a limitation of the claim itself.”¹⁴⁶¹ The recitation of a “method of
3 reducing triglycerides and Apolipoprotein B” in the preamble provides antecedent basis for the
4 effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose
5 for which the method must be performed - to reduce triglycerides and Apolipoprotein B.

6 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
7 to define the subject matter of the claimed invention.”¹⁴⁶² Thus, the entire preamble in the
8 independent claims of the ‘335 must contain patentable weight.

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

12 First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
13 the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of**
14 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
15 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
16 of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and
17 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
18 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
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21 ¹⁴⁶¹ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*
22 *Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
24 necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

¹⁴⁶² *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

1 angina and exercise-induced angina, and destabilization of the angina.”¹⁴⁶³ The invention of WO
2 ‘118 is intended to be administered to any person in need of prevention of the occurrence of
3 cardiovascular events, who are typically hypercholesterolemia patients.¹⁴⁶⁴ WO ‘118 does not
4 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
5 anticipate the independent claims.

6 Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail
7 to prove that these elements of the claimed invention have “strict identity” with the elements of
8 the reference.¹⁴⁶⁵ WO ‘118 fails to anticipate this claim element because the broad disclosure
9 fails to anticipate the narrow claimed range, and the specific patient population defined in the
10 claims is an essential part of the claimed invention.

11 There is no evidence in that subject as described in the claims were ever treated. In fact,
12 WO ‘118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
13 definition of “hypertriglyceridemia” in WO ‘118 to argue that WO ‘118 discloses treatment of
14 the subject as described in the claims. It does not. Defendants’ argument rests on the definition
15 in WO ‘118 of “hypertriglyceridemia” as “fasting serum triglyceride levels of at least 150
16 mg/dL.” WO ‘118’s definition is not tied to a specific subject and there are no working
17 examples, data or other reference in WO ‘118 indicating that any subject with fasting TG levels
18 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
19 EPA at all. In addition, Defendants rely on a reference to “Omacor” in WO ‘118 (at 32) as
20 evidence that a “person of ordinary skill in the art would have understood that the term
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¹⁴⁶³ WO ‘118 at 12.

23 ¹⁴⁶⁴ *Id.*

24 ¹⁴⁶⁵ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of
2 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable
3 and then merely provides examples of commercially available "soft capsules," such as Omacor.
4 The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients
5 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
6 used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably'
7 or 'possibly' meets the claims cannot inherently anticipate as a matter of law."¹⁴⁶⁶ Therefore,
8 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
9 '118 meets the claim elements of the independent claims every time it is administered.

10 Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges
11 claimed by the '335 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
12 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
13 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
14 claimed temperature range, "[g]iven the considerable difference between the claimed range and
15 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
16 claimed range with sufficient specificity to anticipate this element of the claim."¹⁴⁶⁷ A prior art's
17 teaching of a broad genus does not necessarily disclose every species within that genus. The
18 court explained the slightly overlapping range between the preferred range and claimed range "is
19 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"¹⁴⁶⁸ and therefore
20 failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of

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¹⁴⁶⁶ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ¹⁴⁶⁷ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

24 ¹⁴⁶⁸ *Atofina*, 441 F.3d at 1000.

1 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
2 anticipate the subject as described in the claims because it fails to described the claimed TG
3 range with sufficient specificity.

4 The court in *Atofina* ruled on an additional question of anticipation that also involved a
5 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
6 compared to the patent’s claimed range of 0.1 to 5.0 percent.¹⁴⁶⁹ The court explained that
7 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
8 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
9 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”¹⁴⁷⁰ Similarly,
10 although there may be overlap between the definition of hypertriglyceridemia taught by WO
11 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
12 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500
13 mg/dL. In fact, WO ‘118 is directed to compositions and methods for preventing occurrence of
14 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
15 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
16 events as the primary clinical objective),¹⁴⁷¹ WO ‘118, therefore, does not expressly disclose the
17 specific patient population that is an essential element of the claims of the asserted patents.
18 Therefore, WO ‘118 cannot anticipate the claims of the asserted patents.

19 The treatment of a patient with elevated TG levels varies depending on their serum
20 triglyceride levels. Identification of the patient population with very high TG levels (at least 500

22 ¹⁴⁶⁹ *Id.*

23 ¹⁴⁷⁰ *Id.*

24 ¹⁴⁷¹ *See* Section III.

1 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
2 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
3 of lipid disorders.¹⁴⁷² The ATP-III divided hypertriglyceridemia patients into three classes based
4 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
5 and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment
6 strategies for patients depending on classification.¹⁴⁷³ For the borderline-high and high TG
7 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.¹⁴⁷⁴
8 Accordingly, in these populations, physicians focused on lowering LDL-C.¹⁴⁷⁵ In this patient
9 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
10 In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of
11 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated
12 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
13 treatment goal.¹⁴⁷⁶ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
14 were considered fundamentally different from patients with borderline-high or high TGs from a
15 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

16 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
17 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
18 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
19 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
20

21 ¹⁴⁷² *Id.*

22 ¹⁴⁷³ ATP III at 3335; *See also* Section III.

23 ¹⁴⁷⁴ *Id.*

24 ¹⁴⁷⁵ *Id.*

¹⁴⁷⁶ *Id.*

1 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
2 Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels
3 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
4 decreasing triglycerides), as required by the independent claims of the asserted patents, and
5 therefore cannot anticipate the independent claims of the '335 Patent.

6 Third, WO '118 fails to disclose the claim element of "a subject . . . who is not on
7 concomitant statin therapy," or "a subject . . . who is not on concurrent lipid altering therapy."
8 Defendants' only basis for concluding that WO '118 teaches this element is that WO '118
9 "discloses and claims the administration of EPA-E without the administration in combination
10 with statins."¹⁴⁷⁷ This sentence appears to be incomplete, as it is unclear what Defendants mean
11 by "without the administration in combination with statins." This single statement, without
12 citation to a single page in WO '118, fails to demonstrate that WO '118 teaches this element. In
13 fact, WO '118 methods comprise statins, i.e. HMG-CoA RI.¹⁴⁷⁸

14 WO '118 states that its disclosed composition is "effective in preventing occurrence of
15 cardiovascular events in hypercholesterolemia patients, and **in particular**, in preventing
16 occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with
17 HMG-CoA RI but still suffer from the risk of the cardiovascular events."¹⁴⁷⁹ WO '118 goes on
18 to state that the "effect of the composition of the present invention will be synergistically
19 improved by combined use with the HMG-CoA RI, and such use of the composition of the
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¹⁴⁷⁷ Defendants' Invalidity Contentions at 46.

22 ¹⁴⁷⁸ HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of
23 drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

24 ¹⁴⁷⁹ WO '118 at 9 (emphasis added).

1 present invention with the HMG-CoA RI has clinical utility since the effect of preventing the
2 cardiovascular event occurrence is expected to be improved.”¹⁴⁸⁰ Administering the composition
3 of WO ‘118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-
4 CoA RI has on the disclosed compound. Further, WO ‘118 teaches that the disclosed
5 composition may be used with a long list of other drugs, including lipid altering drugs such as
6 antilipotropic drugs and fibrate drugs.¹⁴⁸¹ Thus, WO ‘118 does not disclose administration of the
7 claimed EPA compositions to a subject that has very high TG levels and also “not on
8 concomitant statin therapy” or “not on concurrent lipid altering therapy” and cannot anticipate
9 the independent claims of the ‘335 patent. In fact, the example of the methods of WO ‘118
10 expressly teaches a statin/EPA co-therapy. Because the dependent claims depend from the
11 independent claims, they include the elements of the independent claims. Thus, WO ‘118 cannot
12 anticipate any of the dependent claims of the ‘335 patent.

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

15 WO ‘118 further does not anticipate the claims of the ‘335 patent because it does not
16 disclose “administering orally to the subject.” As WO ‘118 fails to disclose the subject as
17 claimed, it cannot anticipate oral administration to the claimed “subject.”

18 WO ‘118 additionally cannot anticipate the claims of the ‘335 patent because it does not
19 disclose administering the pharmaceutical composition at a dose of about 4g per day.
20 Defendants argue that this element is disclosed by WO ‘118’s teaching that the daily dose is
21 “typically 0.3 to 6 g/day.” Defendants fail to provide the entire disclosure of WO ‘118, which
22 states that the daily dose is “typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more

23 ¹⁴⁸⁰ *Id.* at 10.

24 ¹⁴⁸¹ *Id.* at 24-25.

1 preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8
2 g.day. Another preferable fatty acid included is DHA-E.” WO ‘118 teaches that the dosage is
3 not particularly limited as long as the intended effect, preventing the occurrence of
4 cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose
5 that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be
6 effective to reduce triglycerides in the claimed patient population. Furthermore, there are no
7 working examples, data or other reference in WO ‘118 indicating that any subject (much less
8 one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the
9 asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

10 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
11 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
12 court explained that this slight overlap “is not disclosed as . . . a species of the claimed generic
13 range of 330 to 450 °C,”¹⁴⁸² and therefore failed to anticipate the claimed range. The court in
14 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
15 the patent’s claimed range of 0.1 to 5.0 percent.¹⁴⁸³ The court explained that “although there is a
16 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
17 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
18 different, not the same. . . . Thus, there is no anticipation.”¹⁴⁸⁴ Similarly, although there may be
19 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘335
20 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range

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¹⁴⁸² *Atofina*, 441 F.3d at 1000.

23 ¹⁴⁸³ *Id.*

24 ¹⁴⁸⁴ *Id.*

1 claimed by the '335 patent does not fall within WO '118's preferred range. Defendants
2 conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably,
3 the example indicates that up to 900 mg of the EPA composition could be used three times per
4 day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '335
5 patent and cannot anticipate the independent claims of the '335 Patent.

6 WO '118 further does not anticipate the claims of the '335 patent because it does not
7 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
8 portion of the disclosure and exclude sections that show the breadth of WO '118's teachings.
9 WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high
10 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
11 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
12 higher, and still more preferably 96.5% by weight or higher."¹⁴⁸⁵ Therefore, WO '118 discloses
13 EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total
14 fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed
15 generic range for the EPA composition in the claimed pharmaceutical composition.

16 The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the
17 . . . range claimed in the" patent is insufficient for anticipation.¹⁴⁸⁶ In *Atofina*, the prior art
18 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
19 range between 330 and 450 degrees. The court explained that this slight overlap "is not
20 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"¹⁴⁸⁷ and therefore failed
21

22 ¹⁴⁸⁵ WO '118 at 22.

23 ¹⁴⁸⁶ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

24 ¹⁴⁸⁷ *Atofina*, 441 F.3d at 1000.

1 to anticipate the claimed range.¹⁴⁸⁸ The court in *Atofina* also found that a prior art disclosure of a
2 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
3 percent.¹⁴⁸⁹ The court explained that “although there is a slight overlap, no reasonable fact finder
4 could determine that this overlap describes the entire claimed range with sufficient specificity to
5 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
6 anticipation.”¹⁴⁹⁰

7 Similarly, although there may be some overlap between the E-EPA content disclosed by
8 WO ‘118 and the ranges claimed by the ‘335 patent, WO ‘118 does not specifically highlight the
9 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
10 critical factor of the invention disclosed in the ‘335 patent. Therefore, WO ‘118’s broad
11 disclosure of the E-EPA content in its invention does not describe the claimed range with
12 sufficient specificity and cannot anticipate the independent claims of the ‘335 patent.

13 WO ‘118 is additionally insufficient for anticipation because it does not expressly
14 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO ‘118
15 makes no distinction between EPA and DHA, stating that “[a]nother preferable fatty acid is
16 DHA-E.”¹⁴⁹¹ The disclosure goes on to state that the composition of the invention is preferably
17 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
18 pharmaceutical composition is a critical factor of the invention disclosed in the ‘335 patent.

19 The disclosure of WO ‘118 treats DHA and EPA interchangeably. The disclosed
20 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.

21
22 ¹⁴⁸⁸ *Atofina*, 441 F.3d at 1000.

23 ¹⁴⁸⁹ *Id.*

24 ¹⁴⁹⁰ *Id.*

¹⁴⁹¹ WO ‘118 at 22.

1 There is no express teaching or guidance directing the person of ordinary skill in the art to the
2 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
3 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
4 claims of the '335 patent.

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

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

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

23 Defendants fail to address any of the claim elements of the dependent claims.
24 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail

1 to set forth any meaningful basis for concluding that WO '118 teaches these elements.
2 Defendants further argue that “aspects of the claims relating to effects that are to be achieved by
3 practicing the claimed method represent inherent, natural properties of EPA, and are entitled to
4 no patentable weight.” To the extent the recited claim elements relate to the administration step,
5 the dosage form or characteristics of the treated subject and the specific effect produced by the
6 claimed method, Defendants’ contentions that the claim limitations are inherent properties of
7 EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO
8 '118, they fail to identify any basis, explanation, or even supporting argument for that assertion.
9 Defendants have not met the burden to establish anticipation with the naked assertion that the
10 effects are inherent, natural properties of EPA.

11 Further, Defendants entirely fail to prove that inherently discloses the recited claim
12 limitations. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
13 inherently anticipate as a matter of law.”¹⁴⁹² “[A]nticipation by inherent disclosure is appropriate
14 only when the reference discloses prior art that must *necessarily* include the unstated
15 limitation.”¹⁴⁹³ “It is not sufficient if a material element or limitation is ‘merely probably or
16 possibly present’ in the prior art.”¹⁴⁹⁴ Defendants fail to show that WO '118 “*necessarily*” meets
17 the recited claim elements relating to the administration step, the dosage form or characteristics
18 of the treated subject and the specific effect produced by the claimed method *every time*. WO
19 '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
20 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
21

22 _____
¹⁴⁹² *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

23 ¹⁴⁹³ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

24 ¹⁴⁹⁴ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

1 the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to,
2 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
3 convincing evidence that the composition disclosed by WO '118 meets any dependent claim
4 elements.

5 **3. The Claims of the '335 Patent Would Not Have Been Obvious In**
6 **Light of the Asserted References**

7 Defendants identify 77 separate references that it asserts somehow render the claims of
8 the '335 patent obvious.¹⁴⁹⁵ Defendants fail to demonstrate by clear and convincing evidence
9 that any of these references, alone or in combination, would render obvious any claims of the
10 '335 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of
11 the '335 patent itself to guide its combination of references.¹⁴⁹⁶ Defendants chart a laundry list
12 of 77 separate references, without explanation. Defendants' disclosures do not comply with
13 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
14 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
15 cannot respond to undisclosed combinations and arguments.¹⁴⁹⁷

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

19 ¹⁴⁹⁵ Defendants' Joint Invalidation Contentions at 13-25.

20 ¹⁴⁹⁶ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention
21 as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is
22 obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

23 ¹⁴⁹⁷ This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
24 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 • 1) “. . .the asserted claims of the ’335 patent would have been obvious over the
2 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
3 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
4 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
5 2000.”
- 6 • 2) “. . .the asserted claims of the ’335 patent would have been obvious over the
7 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
8 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
9 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
10 2000 and/or Maki.”
- 11 • 3) “. . .the asserted claims of the ’335 patent would have been obvious over the
12 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
13 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
14 of Satoh or Shinozaki in further view of Contacos.”
- 15 • 4) “. . . the asserted claims of the ’335 patent would have been obvious over WO ’118
16 or WO ’900 in combination with treatment regimen of Lovaza as evidenced by the
17 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”
- 18 • 5) “. . . the asserted claims of the ’335 patent would have been obvious over WO
19 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
20 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
21 further in view of Katayama, Matsuzawa and/or Takaku.”

22 A patent claim is invalid “if the differences between the subject matter sought to be
23 patented and the prior art are such that the subject matter as a whole would have been obvious at
24 the time the invention was made to a person having ordinary skill in the art.”¹⁴⁹⁸ 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.¹⁴⁹⁹

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

¹⁴⁹⁸ 35 U.S.C. § 103(a).

¹⁴⁹⁹ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

1 teaches, including the portions that would lead away from the claimed invention.¹⁵⁰⁰ Indeed, any
2 teaching in the art that points away from the claimed invention must be considered.¹⁵⁰¹ A
3 reference teaches away if a person of ordinary skill, upon reading the reference, would be
4 discouraged from following the path set out in the reference, or would be led in a direction
5 divergent from the path that was taken by the applicant.¹⁵⁰² For instance, a reference teaches
6 away if it suggests that the line of development flowing from the reference’s disclosure is
7 unlikely to be productive of the result sought by the applicant.¹⁵⁰³

8 In order to find obviousness based on a combination of references, there must be some
9 rationale for combining the references in the way claimed that is separate and apart from the
10 hindsight provided by the patented invention itself.¹⁵⁰⁴ The law prohibits an obviousness
11 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
12 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
13 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
14 invention.”¹⁵⁰⁵ “The invention must be viewed not after the blueprint has been drawn by the
15 inventor, but as it would have been perceived in the state of the art that existed at the time the
16 invention was made.”¹⁵⁰⁶

17 “The determination of obviousness is made with respect to the subject matter as a whole,
18

19 ¹⁵⁰⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ¹⁵⁰¹ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

21 ¹⁵⁰² *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

22 ¹⁵⁰³ *Id.*

23 ¹⁵⁰⁴ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

24 ¹⁵⁰⁵ *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

¹⁵⁰⁶ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

1 not separate pieces of the claim.”¹⁵⁰⁷ “[A] patent composed of several elements is not proved
2 obvious merely by demonstrating that each of its elements was, independently, known in the
3 prior art.”¹⁵⁰⁸ “This is so because inventions in most, if not all, instances rely upon building
4 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
5 of what, in some sense, is already known.”¹⁵⁰⁹

6 Accordingly, it is improper to pick and choose isolated elements from the prior art and
7 combine them so as to yield the invention¹⁵¹⁰ or to modify a prior art reference in a way that
8 “would destroy the fundamental characteristics of that reference.”¹⁵¹¹ Moreover, a combination
9 is not obvious where “it would be impossible to apply these teachings [of the secondary
10 reference] to the [primary reference] without entirely changing the basic mechanism and
11 procedure thereof,”¹⁵¹² or where the proposed combination requires “material and radical
12 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
13 prior art device.¹⁵¹³ Furthermore, it is improper “to modify the secondary reference before it is
14 employed to modify the primary reference” in assessing obviousness.¹⁵¹⁴

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18 ¹⁵⁰⁷ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

19 ¹⁵⁰⁸ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

20 ¹⁵⁰⁹ *KSR*, 550 U.S. at 418-419.

21 ¹⁵¹⁰ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

22 ¹⁵¹¹ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

23 ¹⁵¹² *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

24 ¹⁵¹³ *Id.* at 88.

¹⁵¹⁴ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

1 Further, a party asserting obviousness in view of a combination of prior art disclosures
2 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
3 combine the elements in the manner claimed¹⁵¹⁵ and “a reasonable expectation of success.”¹⁵¹⁶

4 For chemical compounds, there must have been a reason both to select the prior art
5 compound “most promising to modify” and to make the necessary changes to arrive at the
6 claimed compound.¹⁵¹⁷ This protects against the use of hindsight to pick through the prior art
7 based solely on structural similarity to the claimed compound.¹⁵¹⁸ Any assertion of an “apparent
8 reason” must find a basis in the factual record.¹⁵¹⁹

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10
11 ¹⁵¹⁵ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
12 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
13 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
14 *Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998).

13 ¹⁵¹⁶ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
14 *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
15 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
16 an unexpected and fruitful manner” would not have been obvious).

15 ¹⁵¹⁷ *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
16 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
17 *Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

17 ¹⁵¹⁸ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
18 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
19 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
20 2002).

19 ¹⁵¹⁹ *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile *KSR* relaxed some of the formalism of earlier decisions
20 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
21 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
22 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
23 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
24 *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”).

1 The “reasonable expectation of success” for a chemical compound must be of all of a
2 claimed compound’s relevant properties,¹⁵²⁰ including those discovered after the patent was filed
3 or even issued.¹⁵²¹ “The basic principle behind this rule is straight-forward—that which would
4 have been surprising to a person of ordinary skill in a particular art would not have been
5 obvious.”¹⁵²² Any assertion of a “reasonable expectation of success” must find a basis in the
6 factual record.¹⁵²³

7 In an obviousness determination, any objective indicia of nonobviousness must be taken
8 into account.¹⁵²⁴ An objective indicium is any “event[] proved to have actually happened in the
9 real world” that evidences the nonobvious nature of the invention.¹⁵²⁵ The existence of an
10 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
11

12
13 ¹⁵²⁰ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
14 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
15 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
16 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
17 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the
18 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
19 pharmacological properties that it possesses.”).

20 ¹⁵²¹ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
21 908.

22 ¹⁵²² *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995) (“The principle applies most often to the less predictable fields,
23 such as chemistry, where minor changes in a product or process may yield substantially different results.”).

24 ¹⁵²³ *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.’”).

¹⁵²⁴ *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).

¹⁵²⁵ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

1 surprising results, expressions of skepticism, industry praise, commercial success, and copying
2 are classical indicia of nonobviousness.¹⁵²⁶ These factual inquiries “guard against slipping into
3 use of hindsight,”¹⁵²⁷ and “may often be the most probative and cogent evidence of
4 nonobviousness.”¹⁵²⁸

5 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
6 have been fully “in possession” of the public—which requires that the claimed invention have
7 been enabled.¹⁵²⁹

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

11 a) General Overview

12 Defendants fail to provide a single prior art reference that discloses administration of the
13 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
14 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
15 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
16 degrees of purity, in a wide range of doses and administration periods, to subjects who have
17

18 ¹⁵²⁶ *Graham*, 383 U.S. at 17–18; *KSR*, 550 U.S. at 406; *U.S. v. Adams*, 383 U.S. 39, 52 (1966); *Merck & Co. v. Teva*
19 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

20 ¹⁵²⁷ *Graham*, 383 U.S. at 36.

21 ¹⁵²⁸ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*
Inc. v. Lamps Plus, Inc., 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

22 ¹⁵²⁹ *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
23 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
24 making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

1 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
2 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
3 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
4 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
5 distinguish between the effect of the placebo from that of the active agent. Studies which
6 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
7 independent effects of EPA and DHA.¹⁵³⁰ Inconsistency in dosages and administration periods
8 and variations in the administered fatty acid compositions also complicate the interpretation of
9 the results and limit the application of these studies.

10 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
11 very high TGs together with patients with high and borderline high TGs indicates that there is no
12 medical difference in responsiveness to treatment among the groups of people.”¹⁵³¹ Defendants
13 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
14 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
15 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
16 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
17 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
18 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
19 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.¹⁵³² In
20

21 ¹⁵³⁰ Mori 2006 at 96.

22 ¹⁵³¹ Defendants’ Joint Invalidity Contentions at 484 (*see* FN 86).

23 ¹⁵³² FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
24 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

1 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
2 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
3 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
4 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
5 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
6 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
7 Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical
8 difference in responsiveness to treatment between the very-high TG patient population and lower
9 TG patient populations merely because there was possibly one patient with baseline TG levels of
10 at least 500 mg/dL.

11 As discussed above in Section III, patients with very-high TG levels were considered
12 fundamentally different from patients with borderline-high or high TGs from a clinical,
13 regulatory, and therapeutic perspective.¹⁵³³ Clinically, the authoritative guidance to physicians
14 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
15 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
16 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
17 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
18 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
19 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for
20 very-high TG patients was TG reduction. This distinction between patients with borderline-
21 high/high TG levels and patients with very high TG levels is also observed on the regulatory
22 level. The FDA recognized the different clinical status of the very-high TG population by

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24 ¹⁵³³ See Bays Jan. 8, 2012 Decl., ¶ 20.

1 approving some drugs specifically for the very-high TG group without granting treatment
2 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).¹⁵³⁴

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

9 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
10 increase LDL-C in very-high TG patients.¹⁵³⁵ The fibrate, Tricor (fenofibrate), for example,
11 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)¹⁵³⁶
12 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).¹⁵³⁷ In
13 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
14 significant increase in LDL-C was observed.¹⁵³⁸ In patients with very-high TGs (mean baseline
15 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).¹⁵³⁹ Similar
16 results were seen with the administration of Lopid (gemfibrozil).¹⁵⁴⁰ The differing effects of

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18 ¹⁵³⁴ See Bays Jan. 8, 2012 Decl., ¶ 22.

19 ¹⁵³⁵ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain roughly the same in high TG group, and increase by around 50% in the very-high TG group).

20 ¹⁵³⁶ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

21 ¹⁵³⁷ *Id.*

22 ¹⁵³⁸ *Id.* See also, Trilipix Label at 27.

23 ¹⁵³⁹ *Id.* See also, Trilipix Label at 27.

24 ¹⁵⁴⁰ See Otvos at 1558 (showing administration of Gemfibrozil to patients with borderline-high baseline TG levels had no impact on LDL-C levels); Manttari at 14 and 16 (stating that the effect of gemfibrozil on LDL-C was dependent on initial TG levels, no change was observed for LDL-C in subjects with high baseline TG levels while subjects with normal or borderline-high baseline TG levels showed significant decreases in LDL-C).

1 fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values
 2 demonstrates how a person of ordinary skill at the time of the invention would have understood
 3 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
 4 parameters in patients with normal, borderline-high or high TG levels would be the same in
 5 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
 6 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
 7 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 8 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 9 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 10 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
Tricor (fenofibrate) ¹⁵⁴¹	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

17 Lovaza/Omacor was (and is) a prescription omega-3 therapy known to have differing
 18 lipid effects depending on the patient’s baseline TG level. When administered to patients with
 19 borderline-high baseline TG levels, Lovaza/Omacor significantly reduced TGs and raised HDL-
 20 C.¹⁵⁴² It had no significant effect on other lipid-related variable, including LDL-C and Apo-

¹⁵⁴¹ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

¹⁵⁴² Chan 2002 I at 2379-81.

1 B.¹⁵⁴³ However, when administered to patients with very-high baseline TG levels, TGs were
2 reduced significantly by nearly 50% while LDL-C increased sharply by nearly 50%.¹⁵⁴⁴
3 Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of
4 Lovaza/Omacor was beneficial.¹⁵⁴⁵

5 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
6 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
7 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
8 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
9 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
10 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
11 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
12 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
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15 ¹⁵⁴³ *Id.*; See also, Westphal at 918.

16 ¹⁵⁴⁴ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

17 ¹⁵⁴⁵ See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω -3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω -3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)”)

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1 VLDL particle conversion.¹⁵⁴⁶ Because normal to high TG patients did not have the large
2 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
3 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
4 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
5 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
6 highest baseline TG levels¹⁵⁴⁷ and did not increase for patients with lower TG levels. Therefore,
7 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
8 borderline-high or high TG patients was *expected*.

9 Defendants contend that “a composition and its properties are inseparable, and therefore
10 do not impart any additional patentability,” and that “all of the limitations regarding the
11 properties of the ethyl EPA compound identified in the claims of the ‘335 patent are inherent to
12 the compound when administered to a human subject.”¹⁵⁴⁸ Inherency may not supply a missing
13 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
14 of ordinary skill in the art.¹⁵⁴⁹ Obviousness is based on what is *known* in the art at the time of the
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17 ¹⁵⁴⁶ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
18 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
19 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
20 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
21 of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
22 decrease in VLDL.”).

23 ¹⁵⁴⁷ Bays 2008 I at 400-402.

24 ¹⁵⁴⁸ Defendants’ Joint Invalidity Contentions at 485.

¹⁵⁴⁹ 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).

1 invention.¹⁵⁵⁰ It was not known or reasonably expected at the time of the claimed invention that
2 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
3 substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and
4 Apo-B necessarily present, or the natural result of the combination of elements explicitly
5 disclosed by the prior art.¹⁵⁵¹ Therefore, inherency does not supply the missing claim elements
6 in the prior art cited by Defendants.

7 Defendants argue that the claims of the '335 patent which contain "a limiting clause, such
8 as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively
9 recited and therefore are not elements.¹⁵⁵² This is incorrect. "There is nothing inherently wrong
10 with defining some part of an invention in functional terms."¹⁵⁵³ When a clause "states a
11 condition that is material to patentability, it cannot be ignored in order to change the substance of
12 the invention."¹⁵⁵⁴ The claim term "to effect" acts as a positive limitation if the term represents
13 "unexpected and improved effects of administration of the claimed compound."¹⁵⁵⁵ In addition,
14 the elements represent unexpected and improved effects of administration of purified EPA,
15 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
16 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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20 ¹⁵⁵⁰ *In re Spormann*, 363 F.2d 444, 448 (CCPA 1966) ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.").

21 ¹⁵⁵¹ See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

22 ¹⁵⁵² Defendants' Joint Invalidity Contentions at 486.

23 ¹⁵⁵³ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

24 ¹⁵⁵⁴ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

¹⁵⁵⁵ *AstraZeneca AB v. Dr. Reddy's Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11-12 (D.N.J. May 18, 2010).

1 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
2 patentable weight.

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

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

12 (1) WO '118

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

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
16 '118 disclose or suggest elements of the '335 Claims. The cited portions of WO '118 do not
17 disclose or suggest these elements at least because they do not disclose or suggest administration
18 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
19 portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition
20 with the recited fatty acid dosage. The cited portions of WO '118 further do not disclose or
21 suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

22 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
23 WO '118 does not disclose or suggest a subject with the recited very high TG level. WO '118
24 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty

1 acid dosage. WO '118 further does not disclose or suggest a method to effect the recited TG
2 reduction in the subject with the claimed TG level. With respect to claim 14, WO '118 does not
3 disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject
4 based on a comparison to a second subject having the recited very high TG levels who has not
5 received the pharmaceutical composition and is not on concomitant statin therapy. With respect
6 to claim 22, WO '118 does not disclose or suggest a method to effect the recited TG and
7 Apolipoprotein B effects in the subject with the recited very high TG levels who is not on
8 concomitant lipid altering therapy based on a comparison to a control subject having the recited
9 very high TG levels who has not received the pharmaceutical composition and is not on
10 concomitant lipid altering therapy.

11 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
12 additional lipid outcome based on a comparison to a second subject with the recited very high
13 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
14 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a
15 comparison to a control subject with the recited very high TG levels who has not received the
16 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
17 fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG
18 level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the
19 recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to
20 Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total
21 cholesterol in the subject with the claimed TG level.

22 (2) WO '900

23 WO '900 describes methods for obtaining EPA-rich compositions.
24

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
2 '900 disclose or suggest elements of the '335 Claims. The cited portions of WO '900 do not
3 disclose or suggest these elements at least because they do not disclose or suggest administration
4 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
5 portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition
6 with the recited fatty acid compositions, dosage, or administration period. The cited portions of
7 WO '900 further do not disclose or suggest a method to effect the recited TG reduction in the
8 subject with the claimed TG level.

9 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
10 WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900
11 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
12 acid compositions, dosage, or administration period. WO '900 further does not disclose or
13 suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

14 With respect to claim 14, WO '900 does not disclose or suggest a method to effect the recited
15 TG and Apolipoprotein B effects in the subject based on a comparison to a second subject having
16 the recited very high TG levels who has not received the pharmaceutical composition and is not
17 on concomitant statin therapy. With respect to claim 22, WO '900 does not disclose or suggest a
18 method to effect the recited TG and Apolipoprotein B effects in the subject based on a
19 comparison to a control subject having the recited very high TG levels who has not received the
20 pharmaceutical composition and is not on concomitant lipid altering therapy.

21 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
22 additional lipid outcome based on a comparison to a second subject with the recited very high
23 TG levels who has not received the claimed pharmaceutical composition. With respect to
24

1 Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to
2 4 times per day. With respect to Claims 5 and 25, this reference does not disclose or suggest the
3 subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not
4 disclose or suggest the subject and the second subject having the recited baseline lipid levels.
5 With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid
6 outcomes based on a comparison to a control subject with the recited very high TG levels who
7 has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and
8 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with
9 the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or
10 suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With
11 respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction
12 in total cholesterol in the subject with the claimed TG level.

13 (3) Contacos

14 Contacos describes a study designed to determine the safety and efficacy of a statin
15 (pravastatin) combined with fish oil either alone or in combination, for the management of
16 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in
17 the claims.

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
19 Contacos disclose or suggest elements of the '335 Claims. The cited portions of Contacos do not
20 disclose or suggest these elements at least because they do not disclose or suggest administration
21 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
22 portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition
23 with the recited fatty acid compositions, dosage, or administration period. The cited portions of
24

1 Contacos further do not disclose or suggest a method of administering the claimed
2 pharmaceutical composition to effect the recited TG reduction.

3 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
4 Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
6 acid compositions, dosage, or administration period. Contacos further does not disclose or
7 suggest a method of administering the claimed pharmaceutical composition to effect the recited
8 TG reduction. With respect to claim 14, Contacos does not disclose or suggest a method to
9 effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a
10 second subject having the recited very high TG levels who has not received the pharmaceutical
11 composition and is not on concomitant statin therapy. With respect to claim 22, Contacos does
12 not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the
13 subject based on a comparison to a control subject having the recited very high TG levels who
14 has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

15 Further, with respect to Claim 2, this reference fails to disclose or suggest the
16 administration of the claimed pharmaceutical composition to effect the claimed additional lipid
17 outcome based on a comparison to a second subject with the recited very high TG levels who has
18 not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this
19 reference does not disclose or suggest administration to the subject 1 to 4 times per day. With
20 respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed
21 pharmaceutical composition to effect the claimed additional lipid outcomes based on a
22 comparison to a control subject with the recited very high TG levels who has not received the
23 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
24

1 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
2 effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference
3 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
4 effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this
5 reference fails to disclose or suggest the administration of the claimed pharmaceutical
6 composition to effect the recited reduction in total cholesterol.

7 (4) Grimsgaard

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

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Grimsgaard disclose or suggest elements of the '335 Claims. The cited portions of Grimsgaard
14 do not disclose or suggest these elements at least because they do not disclose or suggest
15 administration of EPA with the recited purity to a subject with the recited very high TG levels.
16 The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical
17 composition with the recited administration period. The cited portions of Grimsgaard further do
18 not disclose or suggest a method to effect the recited TG reduction in the subject with the
19 claimed TG level.

20 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
21 Grimsgaard does not disclose or suggest a subject with the recited very high TG level.
22 Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the
23 recited administration period. Grimsgaard further does not disclose or suggest a method to effect
24 the recited TG reduction in the subject with the claimed TG level. With respect to claim 14,

1 Grimsgaard does not disclose or suggest a method to effect the recited TG and Apolipoprotein B
2 effects in the subject based on a comparison to a second subject having the recited very high TG
3 levels who has not received the pharmaceutical composition and is not on concomitant statin
4 therapy. With respect to claim 22, Grimsgaard does not disclose or suggest a method to effect
5 the recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels
6 who is not on concomitant lipid altering therapy based on a comparison to a control subject
7 having the recited very high TG levels who has not received the pharmaceutical composition and
8 is not on concomitant lipid altering therapy.

9 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
10 additional lipid outcome based on a comparison to a second subject with the recited very high
11 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
12 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a
13 comparison to a control subject with the recited very high TG levels who has not received the
14 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
15 fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG
16 level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the
17 recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to
18 Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total
19 cholesterol in the subject with the claimed TG level.

20 (5) Hayashi

21 Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for
22 8 weeks. The purity of the composition is not reported. The study was not placebo controlled
23 and was conducted in 28 patients with familial combined hyperlipidemia and a serum trygliceride
24 concentration higher than 150 mg/dl or serum total cholestoral concentration higher than 220

1 mg/dl.

2 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
3 '335 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
4 administration of EPA with the recited purity to a subject with the recited very high TG levels
5 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
6 had a TG level above 400 mg/dl. The cited portions of Hayashi further do not disclose or
7 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
8 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
9 recited TG reduction without substantially increasing LDL-C in a subject with the recited very
10 high TG levels.

11 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted
12 claims), Hayashi does not disclose or suggest a subject with the recited very high TG level.
13 Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the
14 recited fatty acid compositions or dosage. Hayashi further does not disclose or suggest a method
15 of administering the claimed pharmaceutical composition to effect the recited TG reduction in
16 the subject with the claimed TG level. With respect to claim 14, Hayashi does not disclose or
17 suggest a method to effect the recited TG and Apolipoprotein B effects in the subject based on a
18 comparison to a second subject having the recited very high TG levels who has not received the
19 pharmaceutical composition and is not on concomitant statin therapy. With respect to claim 22,
20 Hayashi does not disclose or suggest a method to effect the recited TG and Apolipoprotein B
21 effects in the subject based on a comparison to a control subject having the recited very high TG
22 levels who has not received the pharmaceutical composition and is not on concomitant lipid
23 altering therapy.

24

1 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
2 additional lipid outcome based on a comparison to a second subject with the recited very high
3 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
4 17, this reference does not disclose or suggest the subject and the second subject having the
5 recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest
6 the claimed additional lipid outcomes based on a comparison to a control subject with the recited
7 very high TG levels who has not received the claimed pharmaceutical composition. With respect
8 to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in
9 VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this
10 reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the
11 claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or
12 suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

13 (6) Katayama

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

18 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
19 Katayama disclose or suggest elements of the '335 Claims. The cited portions of Katayama do
20 not disclose or suggest these elements at least because they do not disclose or suggest
21 administration of EPA with the recited purity to a subject with the recited very high TG levels.
22 The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical
23 composition with the recited fatty acid compositions or dosage. The cited portions of Katayama
24

1 further do not disclose or suggest a method of administering the claimed pharmaceutical
2 composition to effect the recited TG reduction in the subject with the claimed TG level.

3 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
4 Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama
5 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
6 acid compositions or dosage. Katayama further does not disclose or suggest a method of
7 administering the claimed pharmaceutical composition to effect the recited TG reduction in the
8 subject with the claimed TG level. With respect to claim 14, Katayama does not disclose or
9 suggest a method to effect the recited TG and Apolipoprotein B effects in the subject based on a
10 comparison to a second subject having the recited very high TG levels who has not received the
11 pharmaceutical composition and is not on concomitant statin therapy. With respect to claim 22,
12 Katayama does not disclose or suggest a method to effect the recited TG and Apolipoprotein B
13 effects in the subject based on a comparison to a control subject having the recited very high TG
14 levels who has not received the pharmaceutical composition and is not on concomitant lipid
15 altering therapy.

16 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
17 additional lipid outcome based on a comparison to a second subject with the recited very high
18 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
19 17, this reference does not disclose or suggest the subject and the second subject having the
20 recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest
21 the claimed additional lipid outcomes based on a comparison to a control subject with the recited
22 very high TG levels who has not received the claimed pharmaceutical composition. With respect
23 to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in
24

1 VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this
2 reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the
3 claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or
4 suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

5 (7) Leigh-Firbank

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

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
10 Leigh-Firbank disclose or suggest elements of the '335 Claims. The cited portions of Leigh-
11 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
12 administration of EPA with the recited purity to a subject with the recited very high TG levels.
13 The cited portions of Leigh-Firbank further do not disclose or suggest the claimed
14 pharmaceutical composition with the recited fatty acid compositions, dosage, or administration
15 period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of
16 administering the claimed pharmaceutical composition to effect the recited TG reduction.

17 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
18 Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-
19 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the
20 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not
21 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
22 the recited TG reduction. With respect to claim 14, Leigh-Firbank does not disclose or suggest a
23 method to effect the recited TG and Apolipoprotein B effects in the subject based on a
24 comparison to a second subject having the recited very high TG levels who has not received the

1 pharmaceutical composition and is not on concomitant statin therapy. With respect to claim 22,
2 Leigh-Firbank does not disclose or suggest a method to effect the recited TG and Apolipoprotein
3 B effects in the subject based on a comparison to a control subject having the recited very high
4 TG levels who has not received the pharmaceutical composition and is not on concomitant lipid
5 altering therapy.

6 Further, with respect to Claim 2, this reference fails to disclose or suggest the
7 administration of the claimed pharmaceutical composition to effect the claimed additional lipid
8 outcome based on a comparison to a second subject with the recited very high TG levels who has
9 not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this
10 reference does not disclose or suggest administration to the subject 1 to 4 times per day. With
11 respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed
12 pharmaceutical composition to effect the claimed additional lipid outcomes based on a
13 comparison to a control subject with the recited very high TG levels who has not received the
14 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
15 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
16 effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference
17 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
18 effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this
19 reference fails to disclose or suggest the administration of the claimed pharmaceutical
20 composition to effect the recited reduction in total cholesterol.

21 (8) Lovaza PDR

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

23 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
24 Lovaza PDR disclose or suggest elements of the '335 Claims. The cited portions of the Lovaza

1 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
2 administration of EPA with the recited purity to a subject with the recited very high TG levels.
3 The cited portions of the Lovaza PDR further do not disclose or suggest the claimed
4 pharmaceutical composition with the recited fatty acid compositions or administration period.
5 The cited portions of the Lovaza PDR further do not disclose or suggest a method of
6 administering the claimed pharmaceutical composition to effect the recited TG reduction.

7 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
8 the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the
9 recited fatty acid compositions or administration period. The Lovaza PDR further does not
10 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
11 the recited TG reduction. With respect to claim 14, the Lovaza PDR does not disclose or suggest
12 a method of administering the claimed pharmaceutical composition to effect the recited TG and
13 Apolipoprotein B effects in the subject based on a comparison to a second subject having the
14 recited very high TG levels who has not received the pharmaceutical composition and is not on
15 concomitant statin therapy. With respect to claim 22, the Lovaza PDR does not disclose or
16 suggest a method of administering the claimed pharmaceutical composition to effect the recited
17 TG and Apolipoprotein B effects in the subject based on a comparison to a control subject
18 having the recited very high TG levels who has not received the pharmaceutical composition and
19 is not on concomitant lipid altering therapy.

20 Further, with respect to Claim 2, this reference fails to disclose or suggest the
21 administration of the claimed pharmaceutical composition to effect the claimed additional lipid
22 outcome based on a comparison to a second subject with the recited very high TG levels who has
23 not received the claimed pharmaceutical composition. With respect to Claim 6, this reference
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1 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
2 effect the claimed additional lipid outcomes based on a comparison to a control subject with the
3 recited very high TG levels who has not received the claimed pharmaceutical composition. With
4 respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of
5 the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect
6 to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the
7 claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect
8 to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the
9 claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

10 (9) Maki

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

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
14 disclose or suggest elements of the '335 Claims. The cited portions of Maki do not disclose or
15 suggest these elements at least because they do not disclose or suggest administration of EPA
16 with the recited purity to a subject with the recited very high TG levels. The cited portions of
17 Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited
18 fatty acid compositions, dosage, or administration period. The cited portions of Maki further do
19 not disclose or suggest a method of administering the claimed pharmaceutical composition to
20 effect the recited TG reduction.

21 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
22 Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does
23 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
24 compositions, dosage, or administration period. Maki further does not disclose or suggest a

1 method of administering the claimed pharmaceutical composition to effect the recited TG
2 reduction. With respect to claim 14, Maki does not disclose or suggest a method to effect the
3 recited TG and Apolipoprotein B effects in the subject based on a comparison to a second subject
4 having the recited very high TG levels who has not received the pharmaceutical composition and
5 is not on concomitant statin therapy. With respect to claim 22, Maki does not disclose or suggest
6 a method to effect the recited TG and Apolipoprotein B effects in the subject based on a
7 comparison to a control subject having the recited very high TG levels who has not received the
8 pharmaceutical composition and is not on concomitant lipid altering therapy.

9 Further, with respect to Claim 2, this reference fails to disclose or suggest the
10 administration of the claimed pharmaceutical composition to effect the claimed additional lipid
11 outcome based on a comparison to a second subject with the recited very high TG levels who has
12 not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this
13 reference does not disclose or suggest administration to the subject 1 to 4 times per day. With
14 respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed
15 pharmaceutical composition to effect the claimed additional lipid outcomes based on a
16 comparison to a control subject with the recited very high TG levels who has not received the
17 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
18 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
19 effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference
20 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
21 effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this
22 reference fails to disclose or suggest the administration of the claimed pharmaceutical
23 composition to effect the recited reduction in total cholesterol.

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(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 '335 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 in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 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 in the subject with the claimed TG level. With respect to claim 14, Matsuzawa does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a second subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant statin therapy. With respect to claim 22, Matsuzawa does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a control subject having the

1 recited very high TG levels who has not received the pharmaceutical composition and is not on
2 concomitant lipid altering therapy.

3 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
4 additional lipid outcome based on a comparison to a second subject with the recited very high
5 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
6 17, this reference does not disclose or suggest the subject and the second subject having the
7 recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest
8 the claimed additional lipid outcomes based on a comparison to a control subject with the recited
9 very high TG levels who has not received the claimed pharmaceutical composition. With respect
10 to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of the
11 claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the subject
12 with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to
13 disclose or suggest the administration of the claimed pharmaceutical composition to effect the
14 recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims
15 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed
16 pharmaceutical composition to effect the recited reduction in total cholesterol in the subject with
17 the claimed TG level.

18 (11) Mori 2000

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

21 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
22 2000 disclose or suggest elements of the '335 Claims. The cited portions of Mori 2000 do not
23 disclose or suggest these elements at least because they do not disclose or suggest administration
24 of EPA with the recited purity to a subject with the recited very high TG levels. The cited

1 portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition
2 with the recited administration period. The cited portions of Mori 2000 further do not disclose or
3 suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

4 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
5 Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000
6 also does not disclose or suggest the claimed pharmaceutical composition with the recited
7 administration period. Mori 2000 further does not disclose or suggest a method to effect the
8 recited TG reduction in the subject with the claimed TG level. With respect to claim 14, Mori
9 2000 does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects
10 in the subject based on a comparison to a second subject having the recited very high TG levels
11 who has not received the pharmaceutical composition and is not on concomitant statin therapy.
12 With respect to claim 22, Mori 2000 does not disclose or suggest a method to effect the recited
13 TG and Apolipoprotein B effects in the subject with the recited very high TG levels who is not
14 on concomitant lipid altering therapy based on a comparison to a control subject having the
15 recited very high TG levels who has not received the pharmaceutical composition and is not on
16 concomitant lipid altering therapy.

17 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
18 additional lipid outcome based on a comparison to a second subject with the recited very high
19 TG levels who has not received the claimed pharmaceutical composition. With respect to
20 Claims 2, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to
21 4 times per day. With respect to Claim 6, this reference fails to disclose or suggest the claimed
22 additional lipid outcomes based on a comparison to a control subject with the recited very high
23 TG levels who has not received the claimed pharmaceutical composition. With respect to
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1 Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-
2 C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this
3 reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the
4 claimed TG level. With respect to Claims 9, 12, 22 and 29, this reference fails to disclose or
5 suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

6 (12) Mori 2006

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

9 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
10 2006 disclose or suggest elements of the '335 Claims. The cited portions of Mori 2006 do not
11 disclose or suggest these elements at least because they do not disclose or suggest administration
12 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
13 portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition
14 with the recited fatty acid compositions, dosage, or administration period. The cited portions of
15 Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction in the
16 subject with the claimed TG level.

17 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
18 Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006
19 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
20 acid compositions, dosage, or administration period. Mori 2006 further does not disclose or
21 suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

22 With respect to claim 14, Mori 2006 does not disclose or suggest a method to effect the recited
23 TG and Apolipoprotein B effects in the subject based on a comparison to a second subject having
24 the recited very high TG levels who has not received the pharmaceutical composition and is not

1 on concomitant statin therapy. With respect to claim 22, Mori 2006 does not disclose or suggest
2 a method to effect the recited TG and Apolipoprotein B effects in the subject based on a
3 comparison to a control subject having the recited very high TG levels who has not received the
4 pharmaceutical composition and is not on concomitant lipid altering therapy.

5 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
6 additional lipid outcome based on a comparison to a second subject with the recited very high
7 TG levels who has not received the claimed pharmaceutical composition. With respect to
8 Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to
9 4 times per day. With respect to Claims 5 and 25, this reference does not disclose or suggest the
10 subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not
11 disclose or suggest the subject and the second subject having the recited baseline lipid levels.
12 With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid
13 outcomes based on a comparison to a control subject with the recited very high TG levels who
14 has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and
15 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with
16 the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or
17 suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With
18 respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction
19 in total cholesterol in the subject with the claimed TG level.

20 (13) Nozaki

21 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
22 purity of the composition is reported as 90%. The study was not placebo controlled and was
23 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
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1 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
2 patient population.

3 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
4 '335 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
5 administration of EPA with the recited purity to a subject with the recited very high TG levels
6 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
7 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
8 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
9 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
10 with the recited very high TG levels.

11 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
12 '335 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least
13 because they do not disclose or suggest administration of EPA with the recited purity to a subject
14 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
15 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
16 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
17 further do not disclose or suggest a method to effect the recited TG reduction without
18 substantially increasing LDL-C.

19 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
20 Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also
21 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
22 compositions or dosage. Nozaki further does not disclose or suggest a method of administering
23 the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the
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1 claimed TG level. With respect to claim 14, Nozaki does not disclose or suggest a method to
2 effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a
3 second subject having the recited very high TG levels who has not received the pharmaceutical
4 composition and is not on concomitant statin therapy. With respect to claim 22, Nozaki does not
5 disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject
6 based on a comparison to a control subject having the recited very high TG levels who has not
7 received the pharmaceutical composition and is not on concomitant lipid altering therapy.

8 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
9 additional lipid outcome based on a comparison to a second subject with the recited very high
10 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
11 17, this reference does not disclose or suggest the subject and the second subject having the
12 recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest
13 the claimed additional lipid outcomes based on a comparison to a control subject with the recited
14 very high TG levels who has not received the claimed pharmaceutical composition. With respect
15 to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in
16 VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this
17 reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the
18 claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or
19 suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

20 (14) Omacor PDR

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

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
23 Omacor PDR disclose or suggest elements of the '335 Claims. The cited portions of the Omacor
24 PDR do not disclose or suggest these elements at least because they do not disclose or suggest

1 administration of EPA with the recited purity to a subject with the recited very high TG levels.
2 The cited portions of the Omacor PDR further do not disclose or suggest the claimed
3 pharmaceutical composition with the recited fatty acid compositions or administration period.
4 The cited portions of the Omacor PDR further do not disclose or suggest a method of
5 administering the claimed pharmaceutical composition to effect the recited TG reduction.

6 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
7 the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the
8 recited fatty acid compositions or administration period. The Omacor PDR further does not
9 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
10 the recited TG reduction. With respect to claim 14, the Omacor PDR does not disclose or
11 suggest a method of administering the claimed pharmaceutical composition to effect the recited
12 TG and Apolipoprotein B effects in the subject based on a comparison to a second subject having
13 the recited very high TG levels who has not received the pharmaceutical composition and is not
14 on concomitant statin therapy. With respect to claim 22, the Omacor PDR does not disclose or
15 suggest a method of administering the claimed pharmaceutical composition to effect the recited
16 TG and Apolipoprotein B effects in the subject based on a comparison to a control subject
17 having the recited very high TG levels who has not received the pharmaceutical composition and
18 is not on concomitant lipid altering therapy.

19 Further, with respect to Claim 2, this reference fails to disclose or suggest the
20 administration of the claimed pharmaceutical composition to effect the claimed additional lipid
21 outcome based on a comparison to a second subject with the recited very high TG levels who has
22 not received the claimed pharmaceutical composition. With respect to Claim 6, this reference
23 fails to disclose or suggest the administration of the claimed pharmaceutical composition to
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1 effect the claimed additional lipid outcomes based on a comparison to a control subject with the
2 recited very high TG levels who has not received the claimed pharmaceutical composition. With
3 respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of
4 the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect
5 to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the
6 claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect
7 to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the
8 claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

9 (15) Satoh

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

13 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
14 Satoh disclose or suggest elements of the '335 Claims. The cited portions of Satoh do not
15 disclose or suggest these elements at least because they do not disclose or suggest administration
16 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
17 portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with
18 the recited fatty acid compositions or dosage. The cited portions of Satoh further do not disclose
19 or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

20 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
21 Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does
22 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
23 compositions or dosage. Satoh further does not disclose or suggest a method to effect the recited
24 TG reduction in the subject with the claimed TG level. With respect to claim 14, Satoh does not

1 disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject
2 based on a comparison to a second subject having the recited very high TG levels who has not
3 received the pharmaceutical composition and is not on concomitant statin therapy. With respect
4 to claim 22, Satoh does not disclose or suggest a method to effect the recited TG and
5 Apolipoprotein B effects in the subject with the recited very high TG levels who is not on
6 concomitant lipid altering therapy based on a comparison to a control subject having the recited
7 very high TG levels who has not received the pharmaceutical composition and is not on
8 concomitant lipid altering therapy.

9 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
10 additional lipid outcome based on a comparison to a second subject with the recited very high
11 TG levels who has not received the claimed pharmaceutical composition. With respect to Claim
12 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a
13 comparison to a control subject with the recited very high TG levels who has not received the
14 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
15 fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG
16 level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the
17 recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to
18 Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total
19 cholesterol in the subject with the claimed TG level.

20 (16) Shinozaki

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

23 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
24 Shinozaki disclose or suggest elements of the '335 Claims. The cited portions of Shinozaki do

1 not disclose or suggest these elements at least because they do not disclose or suggest
2 administration of EPA with the recited purity to a subject with the recited very high TG levels.
3 The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical
4 composition with the recited fatty acid compositions or dosage. The cited portions of Shinozaki
5 further do not disclose or suggest a method to effect the recited TG reduction in the subject with
6 the claimed TG level.

7 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
8 Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki
9 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
10 acid compositions or dosage. Shinozaki further does not disclose or suggest a method to effect
11 the recited TG reduction in the subject with the claimed TG level. With respect to claim 14,
12 Shinozaki does not disclose or suggest a method to effect the recited TG and Apolipoprotein B
13 effects in the subject based on a comparison to a second subject having the recited very high TG
14 levels who has not received the pharmaceutical composition and is not on concomitant statin
15 therapy. With respect to claim 22, Shinozaki does not disclose or suggest a method to effect the
16 recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels who
17 is not on concomitant lipid altering therapy based on a comparison to a control subject having the
18 recited very high TG levels who has not received the pharmaceutical composition and is not on
19 concomitant lipid altering therapy.

20 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
21 additional lipid outcome based on a comparison to a second subject with the recited very high
22 TG levels who has not received the claimed pharmaceutical composition. With respect to
23 Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to
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1 4 times per day. With respect to Claims 5 and 25, this reference does not disclose or suggest the
2 subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not
3 disclose or suggest the subject and the second subject having the recited baseline lipid levels.
4 With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid
5 outcomes based on a comparison to a control subject with the recited very high TG levels who
6 has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and
7 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with
8 the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or
9 suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With
10 respect to Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction
11 in total cholesterol in the subject with the claimed TG level.

12 (17) Takaku

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

15 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
16 Takaku disclose or suggest elements of the '335 Claims. The cited portions of Takaku do not
17 disclose or suggest these elements at least because they do not disclose or suggest administration
18 of EPA with the recited purity to a subject with the recited very high TG levels. The cited
19 portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition
20 with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not
21 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
22 the recited TG reduction in the subject with the claimed TG level.

23 With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims),
24 Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also

1 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
2 compositions or dosage. Takaku further does not disclose or suggest a method of administering
3 the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the
4 claimed TG level. With respect to claim 14, Takaku does not disclose or suggest a method to
5 effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a
6 second subject having the recited very high TG levels who has not received the pharmaceutical
7 composition and is not on concomitant statin therapy. With respect to claim 22, Takaku does not
8 disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject
9 based on a comparison to a control subject having the recited very high TG levels who has not
10 received the pharmaceutical composition and is not on concomitant lipid altering therapy.

11 Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed
12 additional lipid outcome based on a comparison to a second subject with the recited very high
13 TG levels who has not received the claimed pharmaceutical composition. With respect to
14 Claims 5 and 25, this reference does not disclose or suggest the subject having the recited
15 baseline lipid levels. With respect to Claim 17, this reference does not disclose or suggest the
16 subject and the second subject having the recited baseline lipid levels. With respect to Claim 6,
17 this reference fails to disclose or suggest the claimed additional lipid outcomes based on a
18 comparison to a control subject with the recited very high TG levels who has not received the
19 claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference
20 fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG
21 level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the
22 recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to

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1 Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total
2 cholesterol in the subject with the claimed TG level.

3 c) The Prior Art Does Not Render the Claims Obvious

4 Defendants have not identified by clear and convincing evidence that the asserted claims
5 of the '335 patent would have been *prima facie* obvious in light of the references cited, either
6 alone or in combination. As described above, none of the references discloses all of the elements
7 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
8 explanation, and argue they somehow must be combined to render obvious the asserted claims.
9 Where Defendants have failed to make disclosures with the specificity required by Local Patent
10 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
11 claim elements at issue.

12 Defendants' contentions fail to disclose each and every element of the claims of the '335
13 patent. Specifically, Defendants do not contend that the relied upon references disclose the
14 following elements of Claim 14 (and therefore its dependent asserted claims as well): (1) a
15 subject having a fasting baseline triglyceride level of 500 mg/dl to about 2000 mg/dl and *who is*
16 *not on concomitant statin therapy*; or (2) administering the claimed pharmaceutical composition
17 to the recited subject effective to reduce fasting triglycerides by at least 25% and to reduce
18 fasting Apolipoprotein B, *based on a comparison to a second subject* having a baseline
19 triglyceride level of 500 mg/dl to about 2000 mg/dl who has not received the pharmaceutical
20 composition and is not on concomitant statin therapy.

21 In addition, Defendants do not contend that the relied upon references disclose the
22 following elements of Claim 22 (and therefore its dependent claims as well): (1) a subject having
23 a fasting baseline triglyceride level of 500 mg/dl to about 2000 mg/dl and *who is not on*
24 *concomitant lipid altering therapy*; or (2) administering the claimed pharmaceutical composition

1 to the recited subject wherein upon administering the composition to the subject daily for said
2 period of 12 weeks the subject exhibits a reduction in fasting triglycerides of at least about 25%
3 and a reduction in fasting Apolipoprotein B based on a comparison to a control subject having a
4 baseline triglyceride level of 500 mg/dl to about 2000 mg/dl who has not received the
5 pharmaceutical composition and is not on concomitant lipid altering therapy.

6 Therefore, Defendants' prior art combinations cannot render the claims *prima facie*
7 obvious.

8 Facts supporting the non-obviousness of the claims of the '335 patent are discussed in
9 detail below. The objective indicia discussed in Section V.O further demonstrate that the '335
10 patent is not obvious. In short, Defendants have not met their burden of showing that the claims
11 would have been obvious.

12 (1) Defendants Do Not Demonstrate that the Independent
13 Claims of the '335 Patent Would Have Been Obvious

14 (a) Defendants Do Not Demonstrate that a Person of
15 Ordinary Skill in the Art Would Have Had Any
Reason to Replace the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

16 (i) The '335 Patent is not Obvious Over the
17 Omacor PDR/Lovaza PDR, in Combination
with Katayama and/or Matsuzawa, Further
18 in View of Nozaki and/or Hayashi and
Further in View of Leigh-Firbank and/or
Mori 2000

19 With respect to the '335 patent, Defendants present a combination of seven references:
20 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering
21 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or
22

1 Hayashi, and further in view of Leigh-Firbank and/or Mori 2000.”¹⁵⁵⁶ Defendants also present
2 charts purporting to assert that an additional 61 references may be combined in order to render
3 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary
4 skill would combine 61 separate references, they additionally do not identify any motivation for
5 combining these references.^{1557, 1558} Although Defendants need not point to an explicit statement
6 in the prior art motivating the combination of these references, any assertion of an “apparent
7 reason” to combine must find a basis in the factual record.¹⁵⁵⁹ Defendants’ unsupported cobbling
8
9

10 ¹⁵⁵⁶ Defendants’ Joint Invalidity Contentions at 479.

11 ¹⁵⁵⁷ Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as
12 described in the references cited above in section V.B.2 in view of, at least, the references cited in V.B.3 and 4,
13 including, the ’954 publication, WO ’900, WO ’118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Matakai,
14 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,
15 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2000,
16 Mori 2006, Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local
17 Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity
18 Contentions at 478-79.

15 ¹⁵⁵⁸ Defendants’ bare assertion that “the motivation or reason to combine or modify prior art to create invalidating
16 combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,” and that
17 “[c]ommon sense, design incentives, market forces, and the background knowledge possessed by a person having
18 ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or
19 modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
20 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 477-78.

18 ¹⁵⁵⁹ *See, e.g., In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
19 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
20 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
21 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
22 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
23 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
24 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

1 of selective disclosures represents hindsight reconstruction.¹⁵⁶⁰ Defendants’ contentions are no
2 more than an assertion that certain claim elements were known in the prior art. Throughout their
3 contentions, Defendants’ selectively cite to data points in a reference without considering other
4 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
5 that it teaches.¹⁵⁶¹ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

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

16 The proposed combinations do not render the independent claims of the ’335 patent
17 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
18 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
19 package insert specifically) during prosecution.¹⁵⁶²

21 ¹⁵⁶⁰ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
22 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

23 ¹⁵⁶¹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

24 ¹⁵⁶² See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.

1 The analysis of the independent claims of the '335 patent is incorporated into all asserted
2 claims that depend from those claims.

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

7 For an invention to be obvious, there must have been an “apparent reason” to make it.
8 The subject matter of the '335 patent claims would not have been obvious in light of these
9 references because a person of ordinary skill would not have been motivated to purify EPA or
10 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
11 levels without an increase in LDL-C levels.

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

16 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
17 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies
18 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
19 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
20 art would not and could not attribute any observed effect (and the magnitude of that effect) to
21 that of the drug. Any observed effect could be placebo dependent.¹⁵⁶³ As discussed above in
22 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
23 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG

24 _____
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).

¹⁵⁶³See 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.)

1 patients because patients with higher TG levels had different lipid responses compared to
2 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
3 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
4 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary
5 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
6 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
7 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
8 high or high TG patients, was expected. At the priority date of the '335 patent, a person of
9 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
10 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
11 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
12 lowering through increased VLDL particle conversion.

13 Defendants argue that these studies disclose known “clinical benefits” of administering
14 pure EPA, lowering triglycerides without raising LDL-C.¹⁵⁶⁴ This is an incorrect characterization
15 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
16 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
17 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
18 Defendants’ selective citation of LDL-C data from these references represents the improper use
19 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
20 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
21 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
22

23 ¹⁵⁶⁴ Defendants’ Joint Invalidity Contentions at 479-80.
24

1 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
2 lowering of TG levels without increasing LDL-C to be a “clinical benefit[.]” is incorrect.¹⁵⁶⁵ The
3 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
4 would a person of ordinary skill view these references as teaching such a benefit for very-high
5 TG patients.

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

10 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
11 purity of Epadel has varied over time and across different formulations of the product, therefore
12 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
13 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
14 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
15 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
16 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.
17 Nishikawa,¹⁵⁶⁶ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
18 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
19 purity.¹⁵⁶⁷

22 ¹⁵⁶⁵ Defendants’ Joint Invalidity Contentions at 479-80.

23 ¹⁵⁶⁶ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS
Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 ¹⁵⁶⁷ See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

1 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
2 patients. These studies would not have been extrapolated to Western populations because the
3 Japanese diet contains much more fish and has a number of other different attributes. The
4 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
5 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
6 the patient population is exclusively Japanese cannot be generalized to other populations.¹⁵⁶⁸
7 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
8 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
9 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
10 that the Japanese respond differently to lipid lowering agents than Westerners.

11 Defendants rely on Katayama to demonstrate the "known clinical benefits of
12 administering pure EPA - lowering triglycerides without raising LDL-C."¹⁵⁶⁹ However,
13 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
14 treatment in patients with hyperlipidemia.¹⁵⁷⁰ Katayama does not disclose *any* LDL-C related
15 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
16 reference to provide any such disclosure. The only results disclosed by Katayama were a
17 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
18 administered to patients with borderline-high to high TG levels, and its safety for long term use
19 in this patient population.¹⁵⁷¹ In addition to Katayama's lack of disclosure regarding LDL-C,
20

21 ¹⁵⁶⁸ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

22 ¹⁵⁶⁹ Defendants' Joint Invalidity Contentions at 4679.

23 ¹⁵⁷⁰ Katayama at 2.

24 ¹⁵⁷¹ *Id.* at 16.

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

3 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
4 administering pure EPA - lowering triglycerides without raising LDL-C.”¹⁵⁷² However,
5 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
6 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
7 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
8 were evaluated for improvement in serum triglycerides levels.¹⁵⁷³ It is unclear which of the 26
9 patients were included in each separate evaluation; therefore one cannot determine the baseline
10 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
11 of a placebo control makes it less likely that the results of this study can be generalized as an
12 effect on any population as a whole and provides no insight with respect to the very-high TG
13 patient population.

14 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
15 and one participant with TG levels > 1,000 mg/dL.¹⁵⁷⁴ However, when analyzing the lipid
16 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
17 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
18 triglyceride levels.”¹⁵⁷⁵ Fig. 4, which depicts the changes in serum triglycerides, shows that the
19 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
20 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than

21 _____
22 ¹⁵⁷² Defendants’ Joint Invalidity Contentions at 479.

23 ¹⁵⁷³ Matsuzawa at 7 and 19.

24 ¹⁵⁷⁴ *Id.* at 23.

¹⁵⁷⁵ *Id.* at 10.

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

8 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
9 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.¹⁵⁷⁶ The disclosure
10 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
11 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
12 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
13 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
14 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
15 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
16 skill in the art, however, would have expected the same treatment in patients with very high TG
17 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
18 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
19 triglyceride levels.¹⁵⁷⁷ At best, Matsuzawa demonstrates the uncertainty and confusion related to
20 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
21

22 ¹⁵⁷⁶ *Id.* at 11.

23 ¹⁵⁷⁷ *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
24 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
compositions used, or identify the patient populations were observed.

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

3 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
4 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
5 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
6 increases LDL-C.¹⁵⁷⁸ Defendants identify no other basis upon which a person of ordinary skill
7 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
8 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
9 asserted claims of the '335 patent.

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

12 Defendants contend that the asserted claims of the '335 patent would have been obvious
13 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
14 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
15 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
16 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
17 very high TG patient population.

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

23
24 ¹⁵⁷⁸ See, e.g., Rambjor.

1 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
2 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
3 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
4 patient population were abnormally high and would not have relied upon these results. Further,
5 the person of skill in the art would not have looked to this patient population to predict the Apo-
6 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
7 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
8 levels.¹⁵⁷⁹ Nozaki does not provide a motivation or reasonable expectation of success for
9 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
10 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
11 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
12 to the very high TG patient population.

13 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
14 the EPA and the DHA content in the composition that was administered is unknown. A person
15 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
16 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
17 C were not statistically significant.¹⁵⁸⁰ Further, the person of skill in the art would not have
18 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
19 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
20 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
21 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
22

23 ¹⁵⁷⁹ Nozaki at 256.

24 ¹⁵⁸⁰ Hayashi at 26, Table I.

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

3 Further, Hayashi was a small study conducted in only Japanese patients and was not
4 placebo controlled. This study would not have been extrapolated to Western populations
5 because the Japanese diet contains much more fish and has a number of other different attributes.
6 The Japanese consume a higher amount of EPA and DHA in their diets than Western
7 populations. In fact, Defendants' own reference states that the results from studies where the
8 patient population is exclusively Japanese cannot be generalized to other populations.¹⁵⁸¹ The
9 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
10 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
11 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
12 the Japanese respond differently to lipid lowering agents than Westerners.

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

18 (iii) Leigh-Firbank and/or Mori
19 2000 Do Not Disclose
20 Purported Knowledge that
21
22

23 ¹⁵⁸¹ Yokoyama 2007 at 1097 (“Because our population was exclusively Japanese, we cannot generalise our results to
24 other populations.”).

1
2
3 Defendants assert, incorrectly, that “it was known in the art as of February 2009 that
4 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
5 C levels.”¹⁵⁸² Defendants’ caveat of DHA being “alone or in a mixture” is telling that it was *not*
6 known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants
7 rely upon to support this statement does not categorize the increase in LDL-C as a “negative
8 effect” in light of the overall impact of the disclosed composition on all lipid parameters.
9 Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As
10 discussed above in Section III, a person of ordinary skill would not expect the same LDL-C
11 effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—
12 as in very-high TG patients because patients with higher TG levels had different lipid responses
13 compared to patients with lower TG levels. Patients with very-high TG levels were considered
14 fundamentally different from patients with borderline-high or high triglycerides from a lipid
15 chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person
16 of ordinary skill in the art would have expected that fish oils (and other TG lowering agents)
17 would not increase LDL-C substantially in patients with normal to borderline high TG levels, but
18 would substantially increase LDL-C in patients with very high TG levels.

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

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¹⁵⁸² Defendants’ Joint Invalidity Contentions at 482.

1 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
2 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
3 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
4 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
5 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
6 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
7 and DHA.¹⁵⁸³ A person of ordinary skill would understand that studies directed to EPA and
8 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
9 lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-
10 Firbank, because purified EPA and DHA were not administered separately.

11 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
12 effects of EPA and DHA individually, even though it administered a combination of EPA and
13 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
14 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
15 phospholipid EPA were *independently* associated with the decrease in fasting TGs,¹⁵⁸⁴ and DHA
16 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
17 of the art and numerous publications cited by Defendants.¹⁵⁸⁵ It is widely accepted that DHA
18 also has a hypotriglyceridemic effect.

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

22 ¹⁵⁸³ Mori 2006 at 96.

23 ¹⁵⁸⁴ Leigh-Firbank at 440.

24 ¹⁵⁸⁵ See, e.g. Grimsgaard at 654.

1 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
2 away from the claimed invention. “A reference may be said to teach away when a person of
3 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
4 out in the reference, or would be led in a direction divergent from the path that was taken by the
5 applicant.”¹⁵⁸⁶ Although teaching away is fact-dependent, “in general, a reference will teach
6 away if it suggests that the line of development flowing from the reference’s disclosures is
7 unlikely to be productive of the result sought by the applicant.”¹⁵⁸⁷

8 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
9 a more favorable lipid profile than after EPA supplementation.”¹⁵⁸⁸ For example, it states that
10 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
11 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
12 effects on fasting glucose concentrations.”¹⁵⁸⁹ Mori 2000 also states that “[d]espite an increase
13 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
14 be favorable.”¹⁵⁹⁰ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
15 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
16 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
17 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
18 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
19

20 ¹⁵⁸⁶ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

21 ¹⁵⁸⁷ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
22 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
23 (“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

24 ¹⁵⁸⁸ Mori 2000 at 1092.

¹⁵⁸⁹ Mori 2000 at 1088.

¹⁵⁹⁰ Mori 2000 at 1092.

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

6 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it
7 was known that DHA alone was responsible for the increase in LDL-C levels. Further,
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
9 has little effect on LDL-C levels.¹⁵⁹¹ Defendants identify no other basis upon which a person of
10 ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa,
11 Leigh-Firbank and/or Mori 2000.

12 (ii) The '335 Patent is not Obvious Over the
13 Omacor PDR/Lovaza PDR, in Combination
14 with Katayama and/or Matsuzawa, and/or
15 Takaku, Further in View of Nozaki and/or
Hayashi, and Further in View of
Grimsgaard, Mori 2000 and/or Maki

16 With respect to the '335 patent, Defendants present a combination of nine references:
17 "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of
18 administering pure EPA as evidenced by Katayama, Matsuzawa, and/or Takaku, further in view
19 of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."¹⁵⁹²
20 Defendants also present charts purporting to assert that an additional 58 references may be
21 combined in order to render the Claims obvious. Not only do Defendants ignore the
22 improbability that a person of ordinary skill would combine 58 separate references, they

23 ¹⁵⁹¹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ¹⁵⁹² Defendants' Joint Invalidity Contentions at 479-80.

1 additionally do not identify any motivation for combining these references. Although
2 Defendants need not point to an explicit statement in the prior art motivating the combination of
3 these references, any assertion of an “apparent reason” to combine must find a basis in the
4 factual record.¹⁵⁹³ Defendants’ unsupported cobbling of selective disclosures represents
5 hindsight reconstruction.¹⁵⁹⁴ Defendants’ contentions are no more than an assertion that certain
6 claim elements were known in the prior art. Throughout their contentions, Defendants’
7 selectively cite to data points in a reference without considering other disclosures or even the
8 reference as a whole. Each reference, however, must be evaluated for all that it teaches.¹⁵⁹⁵
9 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

10 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
11 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
12 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
13 further do not disclose a method to effect the claimed TG reduction without substantially
14 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
15

16 ¹⁵⁹³ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

¹⁵⁹⁴ 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”).

¹⁵⁹⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
2 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
3 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
4 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
5 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '335
6 patent obvious and Defendants' burden to prove otherwise is especially difficult because the
7 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
8 generally and the Lovaza package insert specifically) during prosecution.¹⁵⁹⁶

9 The analysis of the independent claims of the '335 patent is incorporated into all asserted
10 claims that depend from those Claims.

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

14 For an invention to be obvious, there must have been an “apparent reason” to make it.
15 The subject matter of the '335 patent claims would not have been obvious in light of these
16 references because a person of ordinary skill would not have been motivated to purify EPA or
17 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
18 levels without an increase in LDL-C levels.

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

21
22 _____
23 ¹⁵⁹⁶ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

1
2
3 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
4 “known clinical benefits of administering pure EPA - lowering triglycerides without raising
5 LDL-C.” As discussed in Section V.C.3.c.1.a.i.a.i, incorporated herein by reference, Katayama
6 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
7 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
8 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
9 the LDL-C results obtained were a clinical benefit.

10 Defendants also rely on Grimsgaard to support their assertion that “administration of
11 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”¹⁵⁹⁷ However,
12 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
13 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

14 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
15 administered to people with normal triglyceride levels for 7 weeks.¹⁵⁹⁸ The results from the
16 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
17 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
18 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
19 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
20 better maintained with oil rich in DHA than oil rich in EPA.”¹⁵⁹⁹ Although Grimsgaard states

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22 ¹⁵⁹⁷ Defendants’ Joint Invalidity Contentions at 483.

23 ¹⁵⁹⁸ Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG
24 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

¹⁵⁹⁹ Grimsgaard at 654.

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

3 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
 4 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
 5 LDL-C by EPA, as confirmation "that administration of purified DHA results in increased LDL-
 6 C levels while administration of purified EPA resulted in a decrease in LDL-C levels."¹⁶⁰⁰ The
 7 results of Grimsgaard, reproduced below, show that EPA and DHA's impact on LDL-C were the
 8 same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo's
 9 effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to
 10 baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard's
 11 disclosure highlights the importance of a placebo-controlled study and why results compared
 12 only to baseline may be misleading. This type of exaggeration and misinterpretation of the
 13 results published in the prior art is seen throughout the Defendants' invalidity contentions.

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

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	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 ²	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 ²	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 ²	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ²	0.96 ± 0.13	0.04 ± 0.08 ²	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 $\bar{x} \pm$ SD.

²⁻⁵ One-sample t test of difference between baseline and 7 wk: ³ P < 0.001, ⁴ P < 0.01, ⁵ P < 0.05.

20 Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential
 21 effects on lipoprotein and fatty acid metabolism."¹⁶⁰¹ However, Grimsgaard does not conclude

23 ¹⁶⁰⁰ Defendants' Joint Invalidity Contentions at 482 n.83.

24 ¹⁶⁰¹ Grimsgaard at 657.

1 that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that
2 neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and
3 DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading
4 Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of
5 patients with very-high triglycerides, because net decrease in triglycerides was consistently
6 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared
7 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL
8 cholesterol observed with some n-3 fatty acid supplements.”¹⁶⁰² Grimsgaard makes no such
9 statement regarding LDL-C.

10 Defendants cherry-pick results, regardless of whether the effect is found to be statistically
11 significant compared to placebo, in an attempt to force the studies to support their argument that
12 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
13 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
14 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
15 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
16 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
17 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
18 not have statistically significantly effects on LDL-C compared to placebo.¹⁶⁰³ A person of
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20

21 ¹⁶⁰² Grimsgaard at 654.

22 ¹⁶⁰³In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
23 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
24 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
no impact on LDL-C levels.

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

3 Defendants also rely on Takaku to support their assertion that “clinical benefits of
4 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
5 art.¹⁶⁰⁴ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
6 safety of Epadel (of undisclosed purity)¹⁶⁰⁵ based on long-term administration.¹⁶⁰⁶

7 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
8 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
9 acknowledges that “only a few subjects were examined” and cautions against drawing a
10 conclusion “only from the results of the present study.”¹⁶⁰⁷ Because the study did not include
11 any placebo control, a person of ordinary skill in the art would understand these reports do not
12 provide the ability to conclude that the observed lipid effects would have occurred independent
13 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
14 patients, and a person of ordinary skill would not have expected the results to be applicable to the
15 general population.¹⁶⁰⁸

16 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
17 person of ordinary skill would not have expected the results to be applicable to patients with
18

19 ¹⁶⁰⁴ Defendants’ Joint Invalidation Contentions at 480.

20 ¹⁶⁰⁵ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
21 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
Nakamura at 23 (Epadel with purity > 90%).

22 ¹⁶⁰⁶ Takaku at ICOSAPENT_DFNDT00006834.

23 ¹⁶⁰⁷ Takaku at ICOSAPENT_DFNDT00006897.

24 ¹⁶⁰⁸ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

1 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
2 measurement was not feasible due to “insufficient sample.”¹⁶⁰⁹ It is possible that patients with
3 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
4 calculating LDL-C levels when triglyceride level is above 400 mg/dL.¹⁶¹⁰ Moreover, the study
5 does not provide different LDL-C graphs based on the baseline triglyceride levels.¹⁶¹¹ Therefore,
6 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
7 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
8 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
9 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
10 times.¹⁶¹² Because of this volatility, a person of ordinary skill would not be able to conclude
11 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
12 LDL-C, stating only that the fluctuation in LDL-C was not significant.¹⁶¹³

13 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
14 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
15 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
16 administration of *fish oil* to hypercholesterolemia patients.”¹⁶¹⁴ In contrast, Takaku states merely
17 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
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20 ¹⁶⁰⁹ Takaku at ICOSAPENT_DFNDT00006884.

21 ¹⁶¹⁰ See Matsuzawa at ICOSPENT_DFNDTS00006450.

22 ¹⁶¹¹ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

23 ¹⁶¹² Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

24 ¹⁶¹³ Takaku at ICOSAPENT_DFNDT00006897.

¹⁶¹⁴ Takaku at ICOSAPENT_DFNDT00006897.

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

3 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
4 Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
5 studies cited by Defendants suggest that EPA increases LDL-C.¹⁶¹⁵ Defendants identify no other
6 basis upon which a person of ordinary skill would have sought to combine the Omacor
7 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

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

11 Defendants contend that the asserted claims of the '335 patent would have been obvious
12 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
13 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
14 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
15 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
16 very high TG patient population.

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

24 ¹⁶¹⁵ See, e.g., Rambjor.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
2 patient population were abnormally high and would not have relied upon these results. Further,
3 the person of skill in the art would not have looked to this patient population to predict the Apo-
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
6 levels.¹⁶¹⁶ Nozaki does not provide a motivation or reasonable expectation of success for
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
12 the EPA and the DHA content in the composition that was administered is unknown. A person
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
15 C were not statistically significant.¹⁶¹⁷ Further, the person of skill in the art would not have
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
21 administered to the very high TG patient population.

23 ¹⁶¹⁶ Nozaki at 256.

24 ¹⁶¹⁷ Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not
2 placebo controlled. This study would not have been extrapolated to Western populations
3 because the Japanese diet contains much more fish and has a number of other different attributes.
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western
5 populations. In fact, Defendants' own reference states that the results from studies where the
6 patient population is exclusively Japanese cannot be generalized to other populations.¹⁶¹⁸ The
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
10 the Japanese respond differently to lipid lowering agents than Westerners.

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

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

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
21 C levels."¹⁶¹⁹ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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23 ¹⁶¹⁸ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

24 ¹⁶¹⁹ Defendants' Joint Invalidity Contentions at 482.

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

14 Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known
15 that “DHA was responsible for the increase in LDL-C levels.”¹⁶²⁰ The discussion related to
16 Grimsgaard in Section V.C.3.c.1.a.ii.a.i and Mori 2000 in Section V.C.3.c.1.a.i.a.iii is
17 incorporated herein by reference.

18 Defendants argue that Maki discloses the administration of purified DHA resulted in the
19 desired reduction of TGs, but also significantly increased LDL-C levels.¹⁶²¹ Maki was designed
20 to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with
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22 _____
23 ¹⁶²⁰ Defendants’ Joint Invalidation Contentions at 480.

24 ¹⁶²¹ Defendants’ Joint Invalidation Contentions at 482.

1 below-average levels of HDL-C levels.¹⁶²² The DHA supplemented group was administered
2 capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated,
3 monounsaturated and polyunsaturated fatty acids.¹⁶²³ Therefore, Maki demonstrated that when
4 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average
5 levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is
6 observed.¹⁶²⁴ However, one cannot attribute the rise in LDL-C solely to DHA, because the
7 authors admit that “changes in fatty acid intake other than DHA, particularly palmitate, may have
8 also contributed to the elevation in LDL cholesterol.”¹⁶²⁵ Further, Maki admits that the
9 “mechanism(s) responsible for the changes in the lipid profile associated with DHA
10 supplementation are not fully understood.”¹⁶²⁶ Therefore, the results of Maki are inconclusive as
11 to DHA’s effect alone on LDL-C levels.

12 Defendants mischaracterize the rise in LDL-C associated with the administration of
13 omega-3 fatty acids as being a “negative effect” because they incorrectly focus on only the LDL-
14 C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in
15 LDL-C to be troublesome; Maki states that “the lack of increase in the total/HDL cholesterol
16 ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of
17 cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level
18
19

20 ¹⁶²² Maki at 190.

21 ¹⁶²³ Maki at 191.

22 ¹⁶²⁴ Maki at 195.

23 ¹⁶²⁵ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995).

24 ¹⁶²⁶ Maki at 197.

1 less worrisome.”¹⁶²⁷ Therefore, when one of ordinary skill in the art reviewed all the lipid effects
2 of the DHA-rich algal triglycerides, they would have understood that the increase in LDL-C was
3 “less worrisome” because of the “potentially favorable effects on triglycerides, the
4 triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense
5 particles.”¹⁶²⁸

6 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
7 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
8 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
9 has little effect on LDL-C levels.¹⁶²⁹ Defendants identify no other basis upon which a person of
10 ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama,
11 Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

12 (iii) The ‘335 Patent is not Obvious Over the
13 Omacor PDR/Lovaza PDR, in Combination
14 with Katayama in View of Satoh and/or in
View of Satoh or Shinozaki in Further View
of Contacos

15 With respect to the ‘335 patent, Defendants present a combination of five references: “the
16 Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering
17 pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in
18 further view of Contacos.”¹⁶³⁰ Defendants also present charts purporting to assert that an
19 additional 60 references may be combined in order to render the Claims obvious. Not only do
20

21 ¹⁶²⁷ Maki at 197.

22 ¹⁶²⁸ Maki at 197.

23 ¹⁶²⁹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

24 ¹⁶³⁰ Defendants’ Joint Invalidity Contentions at 480.

1 Defendants ignore the improbability that a person of ordinary skill would combine 60 separate
2 references, they additionally do not suggest any identify for combining these references.
3 Although Defendants need not point to an explicit statement in the prior art motivating the
4 combination of these references, any assertion of an “apparent reason” to combine must find a
5 basis in the factual record.¹⁶³¹ Defendants’ unsupported cobbling of selective disclosures
6 represents hindsight reconstruction.¹⁶³² Defendants’ contentions are no more than an assertion
7 that certain claim elements were known in the prior art. Throughout their contentions,
8 Defendants’ selectively cite to data points in a reference without considering other disclosures or
9 even the reference as a whole. Each reference, however, must be evaluated for all that it
10 teaches.¹⁶³³ Accordingly, Defendants fail to meet their burden to establish *prima facie*
11 obviousness.

12 The Lovaza PDR fails to disclose or even suggest the claimed method of reducing
13 triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty
14 acid compositions or administration period. The Lovaza PDR further does not disclose a method
15

16 ¹⁶³¹ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

¹⁶³² 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”).

¹⁶³³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

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

8 Defendants formulate an obviousness argument that relies on Contacos.¹⁶³⁴ However,
9 Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim
10 element or an “apparent reason” or motivation to combine the elements in the manner
11 claimed,¹⁶³⁵.

12 Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and
13 pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore,
14 Contacos fails to provide motivation to administer purified EPA to a very high TG patient
15 population. Contacos also fails to provide motivation to administer purified EPA to a very high
16 TG patient population.

17 The proposed combinations do not render the independent claims of the ’335 patent
18 obvious and Defendants’ burden to prove otherwise is especially difficult because the PTO
19
20

21 ¹⁶³⁴ *Id.*

22 ¹⁶³⁵ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
23 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
24 *Hantscho Comm. Prods., Inc.*, 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally
2 and the Lovaza package insert specifically) during prosecution.¹⁶³⁶

3 The analysis of the independent claims of the '335 patent is incorporated into all asserted
4 claims that depend from those Claims.

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

8 For an invention to be obvious, there must have been an “apparent reason” to make it.
9 The subject matter of the '335 patent claims would not have been obvious in light of these
10 references because a person of ordinary skill would not have been motivated to purify EPA or
11 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
12 levels without an increase in LDL-C levels.

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

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

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23 ¹⁶³⁶ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

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

3 Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of
4 EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects
5 systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when
6 compared to baseline, there was no significant effect when compared to placebo.¹⁶³⁷

7 Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing
8 LDL-C to be a "clinical benefit" is incorrect.¹⁶³⁸ Satoh does not disclose or suggest that the
9 LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these
10 references as teaching such a benefit for very-high TG patients. As discussed above, one of
11 ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500
12 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art,
13 however, would have expected that fish oils (and other TG lowering agents) would substantially
14 increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to
15 administer purified EPA to a very high TG patient population.

16 Further, Satoh was a small study conducted in only Japanese patients. This study would
17 not have been extrapolated to Western populations because the Japanese diet contains much
18 more fish and has a number of other different attributes. The Japanese consume a higher amount
19 of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference
20 states that the results from studies where the patient population is exclusively Japanese cannot be

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23 ¹⁶³⁷ Satoh at 145.

24 ¹⁶³⁸ Defendants' Joint Invalidation Contentions at 480.

1 generalized to other populations.¹⁶³⁹ The Japanese diet comprises between 8 and 15 times more
2 EPA and DHA than typical the typical Western diet. The Western diet typically consists of
3 higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a
4 person of ordinary skill would understand that the Japanese respond differently to lipid lowering
5 agents than Westerners.

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

8 Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without
9 increasing LDL-C to be a "clinical benefit" is incorrect.¹⁶⁴⁰ Shinozaki says nothing about an
10 LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by
11 Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."¹⁶⁴¹ In
12 addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis
13 upon which a person of ordinary skill would have sought to combine the composition disclosed
14 in Shinozaki.

15 Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion
16 that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by
17 Defendants suggest that EPA increases LDL-C.¹⁶⁴² Defendants identify no other basis upon
18 which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama,
19 Satoh, Shinozaki and/or Contacos.

21 ¹⁶³⁹ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
22 other populations.").

23 ¹⁶⁴⁰ Defendants' Joint Invalidity Contentions at 480.

24 ¹⁶⁴¹ Shinozaki at 107-109.

¹⁶⁴² See, e.g., Rambjor.

(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.”¹⁶⁴³ 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.

¹⁶⁴³ Defendants’ Joint Invalidity Contentions at 482.

1 Defendants rely on Geppert and/or Kelley to demonstrate that it was known that “DHA
2 was responsible for the increase in LDL-C levels.”¹⁶⁴⁴ Both Geppert and Kelley administer
3 DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids.
4 Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the
5 independent effects of DHA because it is not clear how much of the supplement’s effects can be
6 attributed to DHA.¹⁶⁴⁵ For example, Defendants’ own prior art teaches that changes in fatty acid
7 intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.¹⁶⁴⁶

8 In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to
9 normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been
10 convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior
11 studies have shown “[i]nconsistent effects of DHA on LDL cholesterol.”¹⁶⁴⁷ Rather than reading
12 Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior
13 studies cited in Geppert. As such, a person of ordinary skill would have concluded that there
14 was confusion in the art and it was unclear whether DHA increased LDL-C.

15 A person of ordinary skill would have expected that Geppert’s results would be
16 applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA
17 was the only component of fish oil to increase LDL-C. For example, there is no data comparing
18 DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying
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¹⁶⁴⁴ Defendants’ Joint Invalidity Contentions at 480.

22 ¹⁶⁴⁵ See Mori 2006 at 96.

23 ¹⁶⁴⁶ Maki at 197.

24 ¹⁶⁴⁷ Geppert at 784.

1 explain the mechanism of LDL-C increase.¹⁶⁴⁸ A person of ordinary skill would have not
2 expected that EPA and DHA would have different effects on LDL-C based on Geppert.

3 Defendants contend that Kelley shows that DHA was responsible for the increase in
4 LDL-C.¹⁶⁴⁹ In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day
5 of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible
6 for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon
7 associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate
8 therapy.¹⁶⁵⁰ Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in
9 context with the other lipid effects reported in the study. Kelley states that:

10 DHA supplementation may lower the risk of CVD by reducing
11 plasma triacylglycerols; triacylglycerol:HDL; the number of small,
12 dense LDL particles; and mean diameter of VLDL particles. An
13 increase was observed in fasting LDL cholesterol, but it is unlikely
14 this increase is detrimental because no increase was observed in the
15 overall number of LDL particles; actually, there was an 11%
16 reduction that was statistically not significant. The reason LDL
17 cholesterol increased despite no change in LDL particle number was
18 that the LDL particles were made larger and hence more cholesterol
19 rich by DHA treatment.¹⁶⁵¹

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

21 ¹⁶⁴⁸ *Id.*

22 ¹⁶⁴⁹ Defendants’ Joint Invalidity Contentions at 480.

23 ¹⁶⁵⁰ Kelley at 329.

24 ¹⁶⁵¹ Kelley at 329

1 health.”¹⁶⁵² Rather than concluding that DHA was uniquely responsible for a rise in LDL-C
2 levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely
3 beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with
4 negative attributes, a person of ordinary skill would understand that the reference taught towards
5 the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400
6 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the
7 very high TG patient population to be different in terms of their response to lipid therapy,
8 including administration of DHA. A person of ordinary skill in the art would have expected that
9 fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with
10 normal to borderline high TG levels, but a person of ordinary skill in the art would expect a
11 substantial increase in LDL-C in patients with very high TG levels.

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

14 Throughout their contentions, Defendants’ selectively cite to data points in a reference
15 without considering other disclosures or even the reference as a whole. Each reference,
16 however, must be evaluated for all that it teaches.¹⁶⁵³ As is the case with Kelley, Defendants use
17 hindsight to characterize a reference based on LDL-C levels alone without considering the other
18 lipid effects studied, considered and reported.¹⁶⁵⁴ The isolated manner in which Defendants
19 select such data points is not the approach that a person of ordinary skill would have taken at the
20

21 ¹⁶⁵² Kelley at 324, 332.

22 ¹⁶⁵³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹⁶⁵⁴ Kelley at 324 (providing that the objectives of the study were to determine “the effects of DHA supplementation
24 on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean
diameters of these particles in fasting and postprandial plasma.”).

1 time of the invention. Defendants' approach represents the use of impermissible hindsight bias.
2 A person of ordinary skill would take into consideration the entire disclosure of a reference,
3 including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore,
4 without explanation, the other effects of DHA that a person of ordinary skill would consider.
5 With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a
6 favorable effect in hypertriglyceridemic patients.

7 Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was
8 known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore,
9 without explanation, other studies that demonstrate that DHA decreases or has little effect on
10 LDL-C levels.¹⁶⁵⁵ Defendants identify no other basis upon which a person of ordinary skill
11 would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos,
12 Geppert and/or Kelley.

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

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

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24 ¹⁶⁵⁵ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

1 mechanism. The therapies that were available at the time of the invention to treat very-high TGs
2 were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin
3 was associated with a highly undesirable side effects—including “flushing” (or reddening of the
4 face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.¹⁶⁵⁶
5 Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in
6 patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed
7 fibrates in combination with an LDL-C lowering medication such as a statin.¹⁶⁵⁷ However, the
8 risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.¹⁶⁵⁸
9 Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a
10 combination fibrate/statin course of treatment.¹⁶⁵⁹ Finally, Lovaza/Omacor were also effective at
11 reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels
12 for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins
13 in order to mitigate increased LDL-C.

14 In any event, a person of ordinary skill in the art would have understood that omega 3-
15 fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high
16 TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would
17 not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs
18 without increasing LDL-C in very high TG patients:

19 _____
20 ¹⁶⁵⁶ See *id.* at 991-92; McKenney 2007, at 718; ATP-III at 3315 (noting that patients often could not tolerate higher doses of niacin due to side effects).

21 ¹⁶⁵⁷ Bays May 16, 2011 Decl., ¶ 8; Topol, at 71 (noting that in high TG patients “the addition of a statin to a fibrate is often required to achieve LDL-C and non-HDL-C goals”);

22 ¹⁶⁵⁸ See *Id.*; McKenney 2007, at 719 (“[F]ibrates may cause rhabdomyolysis, especially when combined with statins.”).

23 ¹⁶⁵⁹ See *Id.*, ¶ 17
24

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ¹⁶⁶⁰	-20%	+45%
Lovaza/Omacor ¹⁶⁶¹	-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 2000 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.”¹⁶⁶² 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.¹⁶⁶³

¹⁶⁶⁰ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

¹⁶⁶¹ Chan 2002 I at 2381 (Table 3).

¹⁶⁶² Defendants’ Joint Invalidation Contentions at 481-82.

¹⁶⁶³ 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

1 It was well known at the time of the invention that omega-3 fatty acids, including both
2 EPA and DHA, caused significant decrease in the production of VLDL particles and a significant
3 increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3
4 fatty acids worked in part by inhibiting VLDL production and improving the conversion of
5 VLDL particles to LDL.¹⁶⁶⁴ A person of ordinary skill in the art understood that EPA and DHA
6 had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when
7 discussing the TG-lowering mechanism of omega-3 fatty acids.¹⁶⁶⁵ The discussion related to the
8 TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and
9 incorporated herein by reference.

10 In fact, it was well understood that the degree of LDL-C elevation observed with
11 prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG
12 levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels
13 the most in patients with the highest pretreatment TG levels.¹⁶⁶⁶ Therefore, a person of ordinary
14 skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct
15 consequence of lowering triglycerides in patients with TG levels ≥ 500 mg/dL. The rise in LDL-

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20 secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in
patients with very-high triglyceride levels when given prescription omega-3 therapy”); Chan 2003

21 ¹⁶⁶⁴ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
decrease in VLDLs after n-3 fatty acid treatment”)

22 ¹⁶⁶⁵ 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))

23 ¹⁶⁶⁶ *See* Bays 2008 Rx Omega-3 p. 402.
24

1 C was often offset by concurrent treatment with statins.¹⁶⁶⁷ The safety and efficacy of using
2 prescription omega-3 in combination with a statin has been well-established.¹⁶⁶⁸

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

6 Therefore, the final LDL-C concentration may still be in the normal range.¹⁶⁶⁹ Furthermore, it
7 was understood that the overall lipid effect of Lovaza/Omacor was beneficial.¹⁶⁷⁰

8 In two pivotal studies in very-high TG patients, both of which used prospective,
9 randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL
10 levels from baseline 13% (p=0.014) and 5.9% (p=0.057).¹⁶⁷¹ Correspondingly, prescription
11 omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.¹⁶⁷² Therefore,
12 “[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can
13 substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net
14

15 ¹⁶⁶⁷ See Harris 2008 at 14, McKenney at 722.

16 ¹⁶⁶⁸ McKenney at 722-23.

17 ¹⁶⁶⁹ See Westphal at 918, Harris 1997 at 389.

18 ¹⁶⁷⁰ See Pownall at 295 (stating that “[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals
with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol] ester
transfer activity], serum TG and VLDL-C; and increasing serum HDL-C”); Harris 1997 at 389 (stating that “[t]he
19 increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-
high TG] patients. It may not be as problematic as it appears, however,” and “the use of omega-3 fatty acids for the
20 treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute
pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this
21 rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty
acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in
LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by
22 decreased non-HDL-C levels (TC minus HDL-C”).

23 ¹⁶⁷¹ McKenney 2007 at 721 (citing Harris 1997 and Pownall).

24 ¹⁶⁷² McKenney 2007 at 722 (see Fig. 1).

1 effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in
2 patients treated with prescription omega-3 fatty acids.” Prescription omega-3 therapy was also
3 known to alter lipoprotein particle size and composition in a favorable manner by decreasing the
4 number of small, dense LDL particles to larger LDL particles.¹⁶⁷³ Lovaza/Omacor “adversely
5 raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration
6 reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable.”¹⁶⁷⁴
7 Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3
8 fatty acids generally, “for the treatment of severe hypertriglyceridemia may be beneficial not
9 only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention
10 of [coronary heart disease].”¹⁶⁷⁵

11 Therefore, contrary to Defendants’ assertion that “a person of ordinary skill in the art at
12 the time of the claimed inventions would have been motivated to find a therapy that would
13 reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting
14 LDL-C levels,”¹⁶⁷⁶ one of ordinary skill in the art at the time of the invention understood that the
15 rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with
16 very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to
17 increase in very-high TG patients, and in some instances the rise was not concerning because
18 LDL-C is often low in patients with severe hypertriglyceridemia and therefore final
19 concentration would still be in the normal range. When LDL-C levels increased beyond what
20 was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

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22 ¹⁶⁷³ McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

23 ¹⁶⁷⁴ Stalenhoef at 134.

24 ¹⁶⁷⁵ Harris 1997 at 389.

¹⁶⁷⁶ Defendants’ Joint Invalidity Contentions at 481-82.

1 reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of
2 Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to
3 identify any other basis upon which a person of ordinary skill would have been motivated to find
4 a therapy that would reduce TG levels in patients with very-high TG levels without negatively
5 impacting LDL-C levels.

6 Defendants make the conclusory allegation that “routine optimization” by a person of
7 ordinary skill would yield the claimed invention.¹⁶⁷⁷ Defendants, however, have offered no
8 explanation to support that allegation and they further fail to establish any of the required criteria
9 of “routine optimization” or the prerequisites to this argument. They also fail to provide any
10 factual detail to support their allegation and they fail to link the allegation to any particular claim
11 or claim element. Defendants mere allegation constitute an improper placeholder to later
12 advance arguments not disclosed in their contentions as required by the Local Rules. In addition,
13 for the reasons discussed herein, a person of ordinary skill would not be motivated to make the
14 combinations alleged by Defendants and, for the same reasons, it would not be routine to
15 combine such references. Where, for example, defendants argue that it would be routine to go
16 from the high TG patient population to the very high TG patient population,¹⁶⁷⁸ they provide no
17 basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill
18 would have understood these patient populations to be distinct with different impacts of lipid
19 therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would
20 not have considered the dosage modification suggested by defendants to be routine; Defendants’
21 argument to the contrary represents hindsight bias.

22
23 ¹⁶⁷⁷ See, e.g., Defendants’ Joint Invalidation Contentions at 477.

24 ¹⁶⁷⁸ Defendants’ Joint Invalidation Contentions at 486-87.

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

- 4 (v) There Was No Motivation and No
5 Reasonable Expectation of Success in
6 Administering the Claimed EPA
7 Composition to Very High TG Patients to
8 Achieve the Claimed Invention (Including
9 its Apo-B Effects)

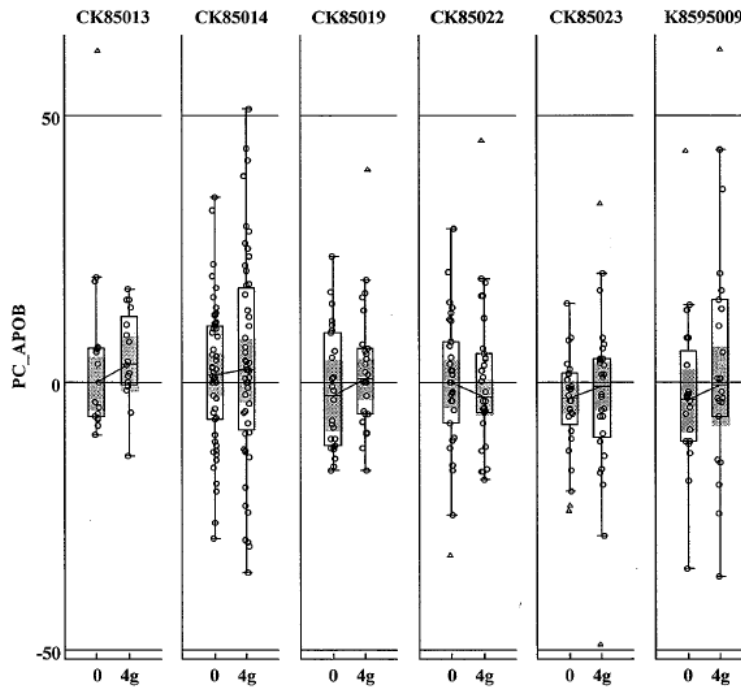
10 A person of skill in the art would *not* have expected that EPA therapy in very high TG
11 patients would yield a reduction in Apo-B levels (which is a reflection of total atherogenic
12 lipoproteins).¹⁶⁷⁹ Accordingly, a person of ordinary skill would *not* have been motivated to
13 administer the claimed EPA therapy to the very high TG population and would *not* have had a
14 reasonable expectation of success in achieving the claimed invention (including its Apo-B
15 effects). A person of ordinary skill would have expected the claimed EPA composition would
16 have similar Apo-B effects as the Lovaza clinical trial—the only clinical trial to study the effects
17 of omega-3 fatty acids on Apo-B levels in patients with very high TG levels.¹⁶⁸⁰ The Lovaza
18 clinical trial, which was a large study conducted on patients with very high TG levels, shows no
19 difference between a placebo-control group and the treatment group with respect to Apo-B
20 levels.¹⁶⁸¹

21
22 _____
¹⁶⁷⁹ *see* Section III.

23 ¹⁶⁸⁰ May 8, 2012 Bays Declaration.

24 ¹⁶⁸¹ Lovaza Approval Package at Table 14.

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

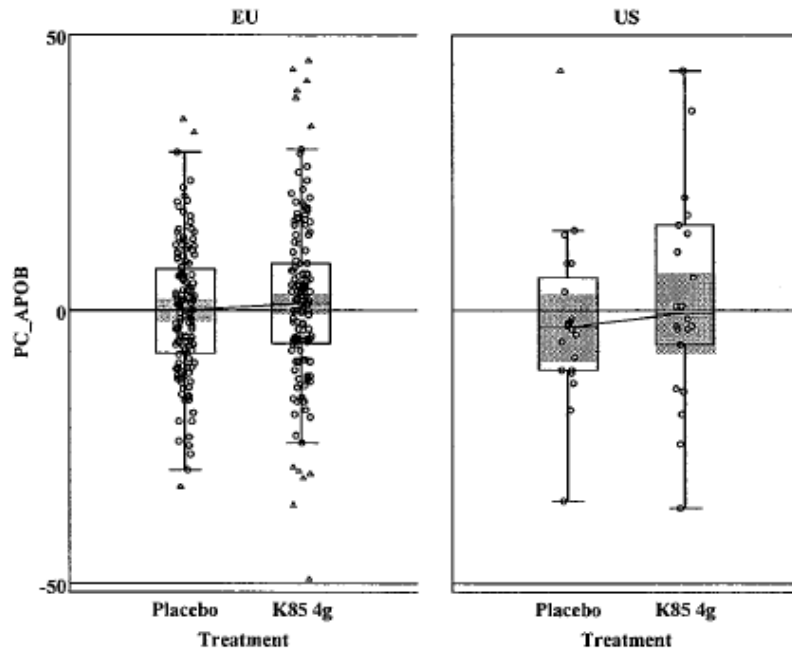


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,¹⁶⁸² there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza did not impact Apo-B compared to placebo.¹⁶⁸³

¹⁶⁸² The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

¹⁶⁸³ 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.¹⁶⁸⁴ 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 not what a person of skill in the art would have expected in light of those references, reflecting a lack of motivation and no reasonable expectation of success.¹⁶⁸⁵

¹⁶⁸⁴ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

¹⁶⁸⁵ Defendants' Contentions at 236.

1 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
2 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.¹⁶⁸⁶ The person of
3 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
4 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
5 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
6 lipoproteins, but instead smaller, denser particles referred to as remnant.¹⁶⁸⁷ Accordingly,
7 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
8 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
9 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
10 would not significantly impact Apo-B.

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

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

18 (i) The '335 Patent is Not Obvious Over WO
19 '118 or WO '900, in Combination With the
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22 _____
23 ¹⁶⁸⁶ ATP-III at 3170; Bays 2008 I at 395.

24 ¹⁶⁸⁷ Kwiterovich in Kwiterovich at 4.

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2
3 With respect to the '335 patent, Defendants present a combination of five references:
4 "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the
5 Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."¹⁶⁸⁸ Defendants also
6 present charts arguing that an additional 61 references may be combined in order to render the
7 Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill
8 would combine 61 separate references, they additionally do not identify any motivation for
9 combining these references.^{1689, 1690} Although Defendants need not point to an explicit statement
10 in the prior art motivating the combination of these references, any assertion of an "apparent
11 reason" to combine must find a basis in the factual record.¹⁶⁹¹ Defendants' unsupported cobbling

12 ¹⁶⁸⁸ Defendants' Joint Invalidity Contentions at 486-87.

13 ¹⁶⁸⁹ Defendants' bare assertion that the asserted claims are obvious "in view of one or more of the references cited in
14 Sections III and V.A and B, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi,
15 Katayama, Matsuzawa, Matakai, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh,
16 Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert,
Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjor, 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 486.

17 ¹⁶⁹⁰ Defendants' bare assertion that "the motivation or reason to combine or modify the prior art to create
18 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,"
19 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 477.

20 ¹⁶⁹¹ See, e.g., *In re Vaidyanathan*, 381 F. App'x 985, 993-94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the
21 formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did
22 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
23 "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.
24 Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants' contention that claims to (+)-citalopram were "*prima*

1 of selective disclosures represents hindsight reconstruction.¹⁶⁹² Defendants’ contentions are no
2 more than an assertion that certain claim elements were known in the prior art. Throughout their
3 contentions, Defendants’ selectively cite to data points in a reference without considering other
4 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all
5 that it teaches.¹⁶⁹³ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

7 WO ‘118 is directed at the composition containing EPA for the purpose of preventing the
8 occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO ‘118
9 is directed, “in particular, [to] preventing occurrence of cardiovascular events in
10 hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the
11 risk of the cardiovascular events.”¹⁶⁹⁴ Contrary to Defendants’ assertion that WO ‘118 discloses
12 “the administration of 4 g of pure EPA with no DHA,”¹⁶⁹⁵ WO ‘118 fails to disclose the claimed
13 subject with the specified very high TG levels who does not receive concurrent lipid altering
14 therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or
15 dosage, or the claimed method to effect the specified TG reduction without substantially
16 increasing LDL-C. WO ‘118 discloses a composition with a wide range of possible EPA

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19 *facie* obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and
20 concluding that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art
would have been motivated to resolve citalopram in June 1988”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

21 ¹⁶⁹² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

22 ¹⁶⁹³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹⁶⁹⁴ WO ‘118 at 9.

24 ¹⁶⁹⁵ Defendants’ Joint Invalidity Contentions at 487.

1 content, dosages, and teaches that DHA is a “preferable fatty acid” to include in the disclosed
2 composition.¹⁶⁹⁶

3 WO ’118 does not disclose administration of highly-purified ethyl-EPA to the target
4 population of the claimed invention. The asserted claims are directed to persons with severe
5 hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO ’118 on the other hand only
6 discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.¹⁶⁹⁷ WO
7 ’118’s emphasis on reducing cardiovascular events suggests that its disclosure is directed to
8 patients with borderline-high to high TG levels, since the primary goal for patients with very-
9 high TG is to prevent acute pancreatitis by decreasing TG levels.¹⁶⁹⁸

10 WO ’118 also does not distinguish EPA from DHA in its disclosures regarding the
11 effectiveness of the substances for treating hypertriglyceridemia.¹⁶⁹⁹ WO ’118 states that
12 “[a]nother preferable fatty acid . . . is DHA-E,” and that “the compositional ratio of EPA-
13 E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E +
14 DHA-E) are not particularly limited as long as intended effects of the present invention are
15 attained.”¹⁷⁰⁰ It further states that “the composition is preferably the one having a high purity of
16 EPA-E and DHA-E.”¹⁷⁰¹ Further, WO ’118 does not disclose EPA’s effect on LDL-C, VLDL-C,
17 Apo-B, or Lp-PLA2.

20 ¹⁶⁹⁶ WO ’118 at 22-23.

21 ¹⁶⁹⁷ WO ’118 at 8.

22 ¹⁶⁹⁸ See Section III.

23 ¹⁶⁹⁹ WO ’118 at 11, 13, 16-21 (“the composition containing at least EPA-E and/or DHA-E as its effective
component”).

24 ¹⁷⁰⁰ WO ’118 at 22-23.

¹⁷⁰¹ WO ’118 at 23.

1 WO '900 is directed to a process for producing purified EPA from a culture of micro-
2 organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels
3 who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition
4 with the specified dosage or administration period, or the claimed method to effect the specified
5 TG reduction without substantially increasing LDL-C. WO '900 only discloses the method of
6 producing purified EPA for therapeutic use, it does not teach *administration* of pure EPA. WO
7 '900 has no discussion, for example, regarding claimed patient population or method of
8 treatment.

9 WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists
10 more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of
11 them.¹⁷⁰² Moreover, WO '900 does not teach the desired effect of EPA other than commenting
12 generally that it “may promote health and ameliorate or even reverse the effects of a range of
13 common diseases.”¹⁷⁰³ It has no discussion, for example, on any TG-lowering effect of EPA.
14 Although WO '900 identifies DHA as an “undesired molecule”, it does not identify the *specific*
15 undesired effect of DHA or other impurities it is trying to prevent other than commenting
16 generally that “the desired effects of EPA may be limited or reversed” by them.¹⁷⁰⁴ It has no
17 discussion related to any LDL-C effects caused by DHA.

18 The proposed combination does not render the independent claims of the '335 patent
19 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
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21

22 ¹⁷⁰² See, e.g., '900 Pub. at 16-17.

23 ¹⁷⁰³ '900 Pub. at 5.

24 ¹⁷⁰⁴ '900 Pub. at 39.

1 considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package
2 insert specifically) during prosecution.¹⁷⁰⁵

3 The analysis of the independent claims of the '335 patent is incorporated into all asserted
4 claims that depend from those Claims.

5 (a) Leigh-Firbank and Mori 2000 Do
6 Not Disclose Purported Knowledge
7 that DHA was Responsible for the
8 Increase in LDL-C

9 Defendants contend that a “person of ordinary skill in the art would have been motivated
10 to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza’s known
11 regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-
12 C levels as evidenced by Leigh-Firbank or Mori 2000.”¹⁷⁰⁶

13 Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with
14 the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need
15 not point to an explicit statement in the prior art motivating the combination of these references,
16 any assertion of an “apparent reason” to combine must find a basis in the factual record.¹⁷⁰⁷

17 ¹⁷⁰⁵ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
18 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
19 Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
20 and convincing standard came into play”).

21 ¹⁷⁰⁶ Defendants’ Joint Invalidity Contentions at 487.

22 ¹⁷⁰⁷ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
23 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
24 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

1 Defendants’ unsupported cobbling of selective disclosures represents hindsight
2 reconstruction.¹⁷⁰⁸ Defendants’ contentions are no more than an assertion that certain claim
3 elements were known in the prior art. Accordingly, Defendants fail to meet their burden to
4 establish *prima facie* obviousness.

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

18 Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants’ assertion that it
19 was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants
20

21 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
22 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

23 ¹⁷⁰⁸ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 ignore, without explanation, other studies that demonstrate that DHA decreases or has little
2 effect on LDL-C levels.¹⁷⁰⁹ Defendants identify no other basis upon which a person of ordinary
3 skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or
4 Mori.

5 (ii) The '335 Patent is not Obvious Over WO
6 '118, WO '900, Grimsgaard, Mori 2000
7 and/or Maki in Combination with the
8 Omacor PDR/Lovaza PDR, and Further in
9 View of Katayama, Matsuzawa and/or
10 Takaku.

11 With respect to the '335 patent, Defendants present a combination of nine references:
12 "WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
13 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view
14 of Katayama, Matsuzawa and/or Takaku."¹⁷¹⁰ Defendants also present charts arguing that an
15 additional 56 references may be combined in order to render the Claims obvious. Not only do
16 Defendants ignore the improbability that a person of ordinary skill would combine 56 separate
17 references, they additionally do not identify any motivation for combining these references.
18 Although Defendants need not point to an explicit statement in the prior art motivating the
19 combination of these references, any assertion of an "apparent reason" to combine must find a
20 basis in the factual record.¹⁷¹¹ Defendants' unsupported cobbling of selective disclosures

21 ¹⁷⁰⁹ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

22 ¹⁷¹⁰ Defendants' Joint Invalidity Contentions at 487.

23 ¹⁷¹¹ See, e.g., *In re Vaidyanathan*, 381 F. App'x 985, 993–94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the
24 formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did
not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi
Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point "must
avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and

1 represents hindsight reconstruction.¹⁷¹² Defendants’ contentions are no more than an assertion
2 that certain claim elements were known in the prior art. Throughout their contentions,
3 Defendants’ selectively cite to data points in a reference without considering other disclosures or
4 even the reference as a whole. Each reference, however, must be evaluated for all that it
5 teaches.¹⁷¹³ Accordingly, Defendants fail to meet their burden to establish *prima facie*
6 obviousness.

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

16 Defendants argue that it “would have been obvious to a person of ordinary skill in the art
17 to use EPA as described in WO ‘118, WO ‘900, Grimsgaard or Mori 2000 in the treatment

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19 _____
20 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
21 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
22 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
23 that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
24 motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

¹⁷¹² 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”).

¹⁷¹³ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR,” but their
2 assertions fail to provide a motivation for combining the references.¹⁷¹⁴ Although Defendants
3 need not point to an explicit statement in the prior art motivating the combination of these
4 references, any assertion of an “apparent reason” to combine must find a basis in the factual
5 record.¹⁷¹⁵ Defendants’ assertions related to motivation are insufficient,¹⁷¹⁶ and accordingly
6 Defendants fail to meet their burden to establish *prima facie* obviousness.

7 Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or
8 Takaku. However, they’ve failed to provide any factual or legal basis as to why each reference
9 discloses a claim element, an “apparent reason” or motivation to combine the elements in the
10 manner claimed.¹⁷¹⁷ Therefore, Defendants should be precluded from relying on this these
11 references.

12
13 ¹⁷¹⁴ Defendants’ Joint Invalidity Contentions at 497.

14 ¹⁷¹⁵ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
15 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
16 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
17 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
18 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
19 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
20 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
21 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
22 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
23 obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
24 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).

¹⁷¹⁶ 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. See Defendants’ Joint Invalidity Contentions at 488. 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.

¹⁷¹⁷ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

1 As discussed above in Section V.C.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only
2 designed to confirm the safety of long term treatment of Epadel and its ability to lower both
3 serum total cholesterol and triglyceride levels. They fail to provide motivation to administer
4 purified EPA to the very high TG patient population. As discussed above in Section
5 V.C.3.c.1.a.ii.a.i, Takaku candidly acknowledges that “only a few subjects were examined” and
6 cautions against drawing a conclusion “only from the results of the present study.”¹⁷¹⁸ Further,
7 the study did not include any placebo control, therefore, a person of ordinary skill in the art
8 would understand these reports do not provide the ability to conclude that the observed lipid
9 effects would have occurred independent of the drug that is administered. In addition, the study
10 was conducted exclusively in Japanese patients, and a person of ordinary skill would not have
11 expected the results to be applicable to the general population.¹⁷¹⁹

12 The proposed combination does not render the independent claims of the '335 patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and
15 Lovaza (both generally and the Lovaza package insert specifically) during prosecution.¹⁷²⁰

16 The analysis of the independent claims of the '335 patent is incorporated into all asserted
17 claims that depend from those Claims.

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

21 ¹⁷¹⁸ Takaku at ICOSAPENT_DFNDT00006897.

22 ¹⁷¹⁹ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.”)

23 ¹⁷²⁰ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012) (taking into account that “the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play”).
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3 Defendants contend that a “person of ordinary skill in the art would have been motivated
4 to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza’s known
5 regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is
6 responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or
7 Maki.”¹⁷²¹

8 Contrary to Defendants’ assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose
9 that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard,
10 Mori 2000 and/or Maki in Section V.C.3.c.1.a.ii.a.iii is incorporated herein by reference. A
11 person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA
12 and DHA’s impact on LDL-C were the same as the effect of the placebo corn oil group; that is,
13 there was no difference between EPA, DHA, or placebo’s effect on LDL-C levels. Although
14 Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not
15 disclose administration of DHA to the requisite patient population and teaches that DHA is
16 preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias,
17 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
18 would consider. Most controlled studies in patients with normal to high baseline TG levels
19 indicated that DHA had little or no effect on LDL-C.¹⁷²² Therefore, a person of ordinary skill
20 would not have concluded that DHA increases LDL-C in patients with normal to high baseline
21 TG levels. Maki demonstrated that when 1.52 g/day DHA and 0.84 g/day palmitic acid is

22 ¹⁷²¹ Defendants’ Joint Invalidity Contentions at 488.

23 ¹⁷²² Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
24 controlled, found an increase in LDL-C after DHA administration.

1 administered to patients with below-average levels of HDL-C levels and borderline-high TG
2 levels, a significant increase in LDL-C is observed.¹⁷²³ However, one of ordinary skill in the art
3 knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.¹⁷²⁴
4 Therefore, the results of Maki are inconclusive as to DHA’s effect alone on LDL-C levels.

5 Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants’ assertion
6 that it was known that DHA was responsible for the increase in LDL-C levels. Further,
7 Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or
8 has little effect on LDL-C levels.¹⁷²⁵ Defendants identify no other basis upon which a person of
9 ordinary skill would have sought to combine WO ‘118, WO ‘900, Grimsgaard, Mori 2000, Maki,
10 the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

15 For an invention to be obvious, there must have been an “apparent reason” to make it.
16 Defendants assert that a “person of ordinary skill in the art would have been motivated to
17 administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to
18 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.”¹⁷²⁶ However, as
19 set forth below, Defendants fail to address why a person of ordinary skill in the art would have

20 ¹⁷²³ Maki at 195.

21 ¹⁷²⁴ Maki at 197; Yu et al., *Plasma Cholesterol-Predictive Equations Demonstrate that Stearic Acid is Neutral and*
22 *Monounsaturated Fatty Acids are Hypocholesterlemic*, 61 AM J CLIN NUTR 1129, 1136 (1995); Weber 2000 (“A
23 number of the earlier-formulated (older) omega-3 fatty acid supplements contained significant amounts of saturated
24 fat and cholesterol, both of which are known to elevate LDL-C.”).

¹⁷²⁵ See e.g., Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

¹⁷²⁶ Defendants’ Joint Invalidity Contentions at 488.

1 been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides
2 greater than or equal to 500 mg/dL.

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

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients
Fibrate ¹⁷²⁷	-20%	+45%
Lovaza/Omacor ¹⁷²⁸	-6%	+45%

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

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

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23 ¹⁷²⁷ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

24 ¹⁷²⁸ Chan 2002 I at 2381 (Table 3).

1 increase LDL-C levels while products containing only EPA did not,” and second, “WO ‘118
2 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-
3 purified ethyl-EPA.”¹⁷²⁹ Both of the “reasons” identified by Defendants are false.

4 Regarding Defendants’ first reason, that “products containing DHA were reported to
5 increase LDL-C levels while products containing only EPA did not,” most controlled studies in
6 patients with normal to high baseline TG levels indicated that DHA had little or no effect on
7 LDL-C.¹⁷³⁰ Therefore, a person of ordinary skill would not have concluded that DHA increases
8 LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley,
9 and Theobald does *not* disclose that “DHA raises LDL-C, an effect associated with heart disease,
10 while EPA does not.”¹⁷³¹ First, Leigh-Firbank cannot comment on the effect of EPA and DHA
11 alone because it did not administer EPA and DHA separately.¹⁷³² A person of ordinary skill
12 would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect
13 of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA
14 on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with
15 other saturated and polyunsaturated fatty acids.¹⁷³³ Therefore, a person of ordinary skill would
16 have known it is unsuitable for evaluating the independent effects of DHA because it is not clear
17 how much of the supplement’s effects can be attributed to DHA.¹⁷³⁴ Kelley does not show that

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¹⁷²⁹ Defendants’ Joint Invalidity Contentions at 488.

20 ¹⁷³⁰ Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo
21 controlled, found an increase in LDL-C after DHA administration.

22 ¹⁷³¹ Defendants’ Joint Invalidity Contentions at 493.

23 ¹⁷³² The discussion related to Leigh-Firbank in Section V.C.3.c.1.a.i.a.iii is incorporated herein by reference.

24 ¹⁷³³ The discussion related to Kelley in Section V.C.3.c.1.a.iii.a.ii is incorporated herein by reference.

¹⁷³⁴ See Mori 2006 at 96.

1 DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a
2 general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase
3 was induced by fibrate therapy.¹⁷³⁵ Kelley specifically teaches that the increase in LDL-C
4 caused by DHA supplementation is unlikely to be “detrimental” because there was not a parallel
5 increase in overall LDL particle number. Rather than concluding that DHA was uniquely
6 responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to
7 disclose that DHA had uniquely beneficial cardioprotective effects.¹⁷³⁶ Finally, Theobald also
8 does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for
9 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by
10 7% when compared to placebo. However, the DHA composition that was administered in
11 Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid,
12 and oleic acid. Therefore, a person of ordinary skill would have known that the DHA
13 administered by Theobald is unsuitable for evaluating the independent effects of DHA because it
14 impossible to determine whether or how much of the supplement’s effects can be attributed to
15 DHA.¹⁷³⁷ Contrary to Defendants’ assertion that there was “a reported advantage to using EPA
16 vs. DHA in hypertriglyceridemic subjects,”¹⁷³⁸ there was no known advantage to using EPA vs.
17 DHA. In fact, a number of the references Defendants cite in their contentions ultimately
18 conclude that DHA supplementation “may represent a more favorable lipid profile than after
19

20 ¹⁷³⁵ Kelley at 329.

21 ¹⁷³⁶ Kelley at 324, 332 (Kelley’s ultimate conclusion is that “[o]verall, DHA supplementation reduced the
22 concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins”
and that “DHA supplementation may improve cardiovascular health.”)

23 ¹⁷³⁷ See Mori 2006 at 96.

24 ¹⁷³⁸ Defendants’ Joint Invalidity Contentions at 488.

1 EPA supplementation.”¹⁷³⁹ In addition, a person of ordinary skill would have recognized any
2 impact of DHA reported by the study to be applicable to EPA because they would have
3 understood these substances to function by the same mechanism. Furthermore, as discussed
4 above in Section III, a person of ordinary skill would not expect the same LDL-C effect in
5 patients with lower baseline TG levels, including healthy patients, as in very-high TG patients
6 because patients with higher TG levels had different lipid responses compared to patients with
7 lower TG levels.

8 Regarding Defendants’ second reason, that “WO ‘118 reports a reduction in
9 cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA,”
10 the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been
11 well documented.¹⁷⁴⁰ Lovaza/Omacor has been shown to reduce the risk for cardiovascular
12 death plus nonfatal myocardial infarction and nonfatal stroke.¹⁷⁴¹ Omega-3 fatty acids have been
13 shown to exert cardioprotective effects in both primary and secondary coronary heart disease
14 prevention trials.¹⁷⁴² Omega-3 fatty acids were known to reduce TG concentration, have
15 antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure
16 and/or reduce heart rate.¹⁷⁴³

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19 ¹⁷³⁹ Mori 2000 at 1092.

20 ¹⁷⁴⁰ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the n-3 FA
and CHD risk.”) (“Harris 2007”); Bays 2008 II at 229-230.

21 ¹⁷⁴¹ See Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*,
98 AM. J. CARDIOL 71i (2006) (“Bays 2006”).

22 ¹⁷⁴² Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*,
197 Atherosclerosis 12, 13 (2008) (“Harris 2008”).

23 ¹⁷⁴³ Harris 2008 at 13.
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1 Defendants argue that a “person of ordinary skill in the art would have appreciated the
2 fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce
3 cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of
4 replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO ‘118.”¹⁷⁴⁴ As
5 discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA
6 and Lovaza/Omacor have been well documented.¹⁷⁴⁵

7 In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart
8 disease endpoints as a function of tissue FA composition found that the evidence suggested that
9 DHA is *more* cardioprotective than EPA.¹⁷⁴⁶ This study found that “depressed levels of long-
10 chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary
11 heart disease events.”¹⁷⁴⁷ Further, the study found that DHA levels, with or without EPA, were
12 significantly lower in fatal endpoints.¹⁷⁴⁸ This study suggests that DHA is preferable to EPA—
13 thus teaching away from the claimed invention.¹⁷⁴⁹ Defendants rely on hindsight bias to argue
14 that a person of ordinary skill would have been motivated to use purified EPA, when both EPA
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16 ¹⁷⁴⁴ Defendants’ Joint Invalidity Contentions at 489.

17 ¹⁷⁴⁵ Harris et al., *Tissue n-3 and n-6 Fatty Acids and Risk for Coronary Heart Disease Events*, 193
ATHEROSCLEROSIS, 1, 8 (2007) (“Overall, these findings confirm the well-known relationship between the *n*-3 FA
18 and CHD risk.”) (“Harris 2007”).

19 ¹⁷⁴⁶ Harris 2007 at 8.

20 ¹⁷⁴⁷ *Id.*

21 ¹⁷⁴⁸ Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 (“Low DHA was the most common finding across all
22 studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.”).

23 ¹⁷⁴⁹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of
24 ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the
reference, or would be led in a direction divergent from the path that was taken by the applicant.”); *see also*
Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs.,*
Inc. v. Garlock, Inc., 721 F.2d 1540, 1552 (Fed. Cir. 1983) (“[P]roceed[ing] contrary to the accepted wisdom of the
prior art ... is strong evidence of nonobviousness.”).

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

3 Defendants argue that the following claim elements were known: the administration of
4 highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the
5 administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to
6 patients with high and very high TG levels who were not receiving concurrent lipid altering
7 therapy, and the dose of 4g/day and 12-week regimen.¹⁷⁵⁰ Defendants then argue that the “only
8 question is whether one skilled in the art would have been motivated to use the DHA-free,
9 highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at
10 least 500 mg/dL as part of the claimed dosage regimen.”¹⁷⁵¹

11 Defendants’ contentions are no more than a recitation that certain claim elements were
12 known in the prior art. Defendants’ assertions to the contrary represent hindsight
13 reconstruction.¹⁷⁵² Notably, Defendants *do not* assert that a person of ordinary skill would have
14 known that purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL),
15 *would not substantially increase LDL-C*. Further, Defendants point to three Japanese studies,¹⁷⁵³
16 which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that “a
17 number of prior art references disclosed the administration of purified EPA to patients with TG
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¹⁷⁵⁰ Defendants’ Joint Invalidity Contentions at 490.

21 ¹⁷⁵¹ Defendants’ Joint Invalidity Contentions at 491.

22 ¹⁷⁵² See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
23 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

24 ¹⁷⁵³ Nakamura, Matsuzawa, and Takaku.

1 levels > 500 mg/dL.”^{1754, 1755} The disclosures of Nakamura (one patient), Matsuzawa (disclosure
2 of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the
3 assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of
4 ordinary skill in the art would *not* understand these references to relate to the use of EPA in
5 patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions
6 regarding these references in terms of the very high TG patient population. In Nakamura, one
7 patient had a baseline TG level > 500 mg/dL.¹⁷⁵⁶ However, the mean baseline TG for all patients
8 was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was
9 well below 500 mg/dL.¹⁷⁵⁷ In Matsuzawa, three patients had TG levels between 400 and 1000
10 mg/dL and one patient had TG levels > 1,000 mg/dL.¹⁷⁵⁸ Based on this disclosure, only one
11 patient definitively had a baseline TG level \geq 500 mg/dL. Further, this one patient was excluded
12 when analyzing the lipid impact because he was a “heavy drinker” and the “effect of alcohol
13 made it impossible to assess triglyceride levels.”¹⁷⁵⁹ In Takaku, three patients had baseline TG
14 levels above 500 mg/dL.¹⁷⁶⁰ However, the mean baseline TG level for all patients was 245
15 mg/dL.¹⁷⁶¹ Indeed, the mean baseline TG level of the patients in all three studies was well below
16

17 ¹⁷⁵⁴ Defendants’ Joint Invalidity Contentions at 490.

18 ¹⁷⁵⁵ Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500
19 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually
20 high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically
21 states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

22 ¹⁷⁵⁶ Nakamura at 23, Table 1.

23 ¹⁷⁵⁷ Nakamura at 23, Tables 1 and 2.

24 ¹⁷⁵⁸ *Id.* at 23.

¹⁷⁵⁹ *Id.* at 10.

¹⁷⁶⁰ Takaku at ICOSAPENT_DFNDTS00006895.

¹⁷⁶¹ Takaku at ICOSAPENT_DFNDTS00006875.

1 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be
2 applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies,
3 patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the
4 Friedewald's Equation cannot be used for patients with triglyceride levels \geq 400 mg/dL.¹⁷⁶²
5 Defendants have failed to identify all of the claimed elements and fail to provide motivation to
6 use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with
7 triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

8 Defendants contend that a "person of ordinary skill in the art would have been motivated
9 to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the
10 known TG-lowering effects of highly-purified EPA-E."¹⁷⁶³ This argument is flawed. The prior
11 art demonstrates a wide range of administration periods utilized in different clinical studies. For
12 example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in
13 Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007.
14 Given the large number of choices of administration periods disclosed in prior art, Defendants
15 have not shown that a person of ordinary skill would not have been motivated to administer
16 highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

17 Moreover, a person of ordinary skill would not have been motivated to administer highly-
18 purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as
19 Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood
20 triglycerides.¹⁷⁶⁴ In fact, Defendants acknowledge in their Joint Invalidation Contentions that

22 ¹⁷⁶² See Matsuzawa at ICOSAPENT_DFNDTS00006450.

23 ¹⁷⁶³ Defendants' Joint Invalidation Contentions at 491.

24 ¹⁷⁶⁴ Mori 2006 at 98.

1 “DHA and EPA were both known to comparably reduce triglycerides, independently of one
2 another.”¹⁷⁶⁵ Data from some studies even suggested that DHA or fish oil may reduce
3 triglyceride more effectively than EPA.¹⁷⁶⁶ Therefore, a person of ordinary skill would not have
4 been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination
5 of EPA and DHA (such as Lovaza) for 12 weeks.

6 Defendants argue that a “person of ordinary skill in the art also would have been
7 motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant
8 reduction in TG that was achieved in six weeks of treatment,” citing Mori 2000.¹⁷⁶⁷ This
9 argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with
10 *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to
11 administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks.

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

15 Defendants further argue that “because Katayama and Saito 1998 teach that higher doses
16 of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of
17 ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a
18 dose of 4 g/day rather than a lower dose.”¹⁷⁶⁸ A person of ordinary skill would not have relied
19 on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,
20

21 ¹⁷⁶⁵ Defendants’ Joint Invalidation Contentions at 495.

22 ¹⁷⁶⁶ Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor
(showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was
greater with DHA supplementation than EPA supplementation).

23 ¹⁷⁶⁷ Defendants’ Joint Invalidation Contentions at 491.

24 ¹⁷⁶⁸ Defendants’ Joint Invalidation Contentions at 491.

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

4 Moreover, as discussed above, it was well known that both EPA and DHA reduced blood
5 triglycerides.¹⁷⁶⁹ Therefore, a person of ordinary skill would not have been motivated to
6 administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of
7 EPA and DHA (such as Lovaza).

8 Defendants further argue that a “person of ordinary skill in the art would have also been
9 motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with
10 highly-purified EPA-E, as suggested by Yokoyama’s teaching that TG was reduced to a much
11 greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito
12 treated subjects having baseline triglyceride levels greater than 500 mg/dl.”¹⁷⁷⁰ This argument is
13 incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a
14 patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have
15 been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3
16 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline
17 TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a
18 greater decrease in TG levels, in the very high TG patient population, would lead to a greater
19 increase in LDL-C levels.

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

22 _____
23 ¹⁷⁶⁹ See Section III.

24 ¹⁷⁷⁰ Defendants’ Joint Invalidity Contentions at 491-92.

1 reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to
2 effect a reduction in TG and LDL-C, if treatment was with statin therapy.”¹⁷⁷¹ Defendants first
3 support this argument by asserting that a person of ordinary skill in the art would have known
4 that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is
5 incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA
6 to raise LDL-C levels in very high TG patients. Defendants’ broadly cite to “Yokoyama 2003,
7 Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in
8 V.B.4. and 5” to support this proposition,¹⁷⁷² however these references do not disclose or suggest
9 to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very
10 high TG patients.¹⁷⁷³

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

16 Defendants argue that a person of ordinary skill in the art “would have known that an
17 increase in LDL-C was an adverse health effect to be avoided.”¹⁷⁷⁴ While an increase in LDL-C
18 was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that
19
20

21 _____
¹⁷⁷¹ Defendants’ Joint Invalidation Contentions at 493.

22 ¹⁷⁷² Defendants’ Joint Invalidation Contentions at 493.

23 ¹⁷⁷³ *See* Section IV.

24 ¹⁷⁷⁴ Defendants’ Joint Invalidation Contentions at 495.

1 the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3
2 fatty acids generally, was related to increased conversion of VLDL to LDL particles.¹⁷⁷⁵

3 Defendants rely on Kelley and the Lovaza label to argue that “one of ordinary skill in the
4 art would have been motivated, with a reasonable expectation of success, to administer a highly-
5 purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in
6 LDL-C with DHA.”¹⁷⁷⁶ However, a person of ordinary skill in the art expected an increase in
7 LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time
8 of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant
9 decrease in the production of VLDL particles and a significant increase in the conversion of
10 VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by
11 inhibiting VLDL production and improving the conversion of VLDL particles to LDL.¹⁷⁷⁷ A
12 person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering
13 mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering
14 mechanism of omega-3 fatty acids.¹⁷⁷⁸ The discussion related to the TG-lowering mechanism of
15 omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

16 Accordingly, a person of ordinary skill would not have been motivated to combine WO
17 '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and
18 Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not
19

20 ¹⁷⁷⁵ See Bays 2008 I at 402; McKenny 2007 at 720 (finding that “[t]hese results illustrate that with prescription
21 omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly
22 converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride
23 levels when given prescription omega-3 therapy”); Chan 2003.

22 ¹⁷⁷⁶ Defendants’ Joint Invalidity Contentions at 495.

23 ¹⁷⁷⁷ Chan 202 at 2378-84; *see also* Westphal at 917 (stating “our data confirm the well-known and pronounced
24 decrease in VLDLs after n-3 fatty acid treatment”).

24 ¹⁷⁷⁸ Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

1 have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-
2 Firbank and/or Mori 2000.

- 3 (iv) There Was No Motivation and No
4 Reasonable Expectation of Success in
5 Administering the Claimed EPA
6 Composition to Very High TG Patients to
7 Achieve the Claimed Invention (Including
8 its Apo-B Effects)

9 A person of skill in the art would *not* have expected that EPA therapy in very high TG
10 patients would yield a reduction in Apo-B levels (which is a reflection of total atherogenic
11 lipoproteins).¹⁷⁷⁹ Accordingly, a person of ordinary skill would *not* have been motivated to
12 administer the claimed EPA therapy to the very high TG population and would *not* have had a
13 reasonable expectation of success in achieving the claimed invention (including its Apo-B
14 effects).

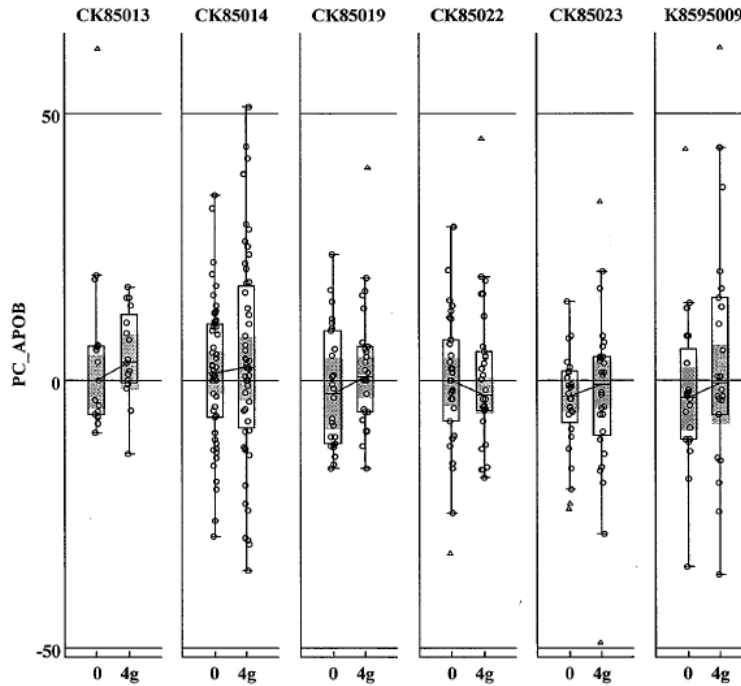
15 A person of ordinary skill would have expected the claimed EPA composition would
16 have similar Apo-B effects as the Lovaza clinical trial—the only clinical trial to study the effects
17 of omega-3 fatty acids on Apo-B levels in patients with very high TG levels.¹⁷⁸⁰ The Lovaza
18 clinical trial, which was a large study conducted on patients with very high TG levels, shows no
19 difference between a placebo-control group and the treatment group with respect to Apo-B
20 levels.¹⁷⁸¹

21
22 _____
¹⁷⁷⁹See Section III.

23 ¹⁷⁸⁰ May 8, 2012 Bays Declaration.

24 ¹⁷⁸¹ Lovaza Approval Package at Table 14.

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

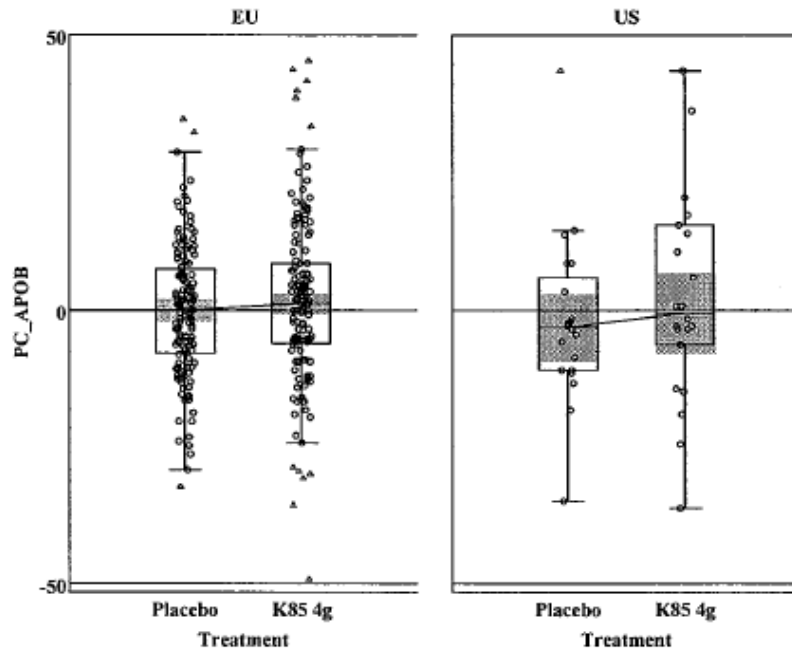


In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,¹⁷⁸² there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza did not impact Apo-B compared to placebo.¹⁷⁸³

¹⁷⁸² The parameters for each study reports can be located at page 4 of the Lovaza Approval Package.

¹⁷⁸³ 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.¹⁷⁸⁴ 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 not what a person of skill in the art would have expected in light of those references, reflecting a lack of motivation and no reasonable expectation of success.¹⁷⁸⁵

¹⁷⁸⁴ See Grimsgaard, Okumura, Hayashi, Hayasaka 1995, and Aoki 1993.

¹⁷⁸⁵ Defendants' Contentions at 236.

1 Further, a person of skill in the art would have understood Apo-B to be a surrogate for the
2 number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.¹⁷⁸⁶ The person of
3 skill in the art would also have recognized that, as TG levels in patients with very high TG levels
4 rose, an increasing amount of TGs in those patients were contained within chylomicrons. As
5 discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic
6 lipoproteins, but instead smaller, denser particles referred to as remnant.¹⁷⁸⁷ Accordingly,
7 because very high TG patients had increasing levels of TGs stored in chylomicrons and because
8 chylomicron processing would not have been understood to yield changes in Apo-B, a person of
9 skill in the art would have believed that TG-lowering therapies directed to very high TG patients
10 would not significantly impact Apo-B.

11 Defendants contend that it was “known in the art that Apo-B proteins are components of
12 LDL and VLDL molecules” but do not cite any prior art to support that proposition, instead
13 relying on a declaration by Dr. Bays and ignoring that Apo-B is associated with all atherogenic
14 lipoproteins, including IDL as discussed in Section III, above. Defendants then cite to Kelley for
15 the proposition that it was known that DHA supplementation decreases VLDL diameter and
16 increases the concentrations of small VLDL particles. Subsequently, they argue that because of
17 the increase in small VLDL particles, a person of skill in the art would expect that DHA therapy
18 would increase Apo-B. That is incorrect. As discussed above, *see* Section III, Apo-B is
19 associated with all atherogenic lipoproteins, not simply small VLDL particles. Defendants also
20 assert that DHA was known to increase LDL-C levels, which is incorrect for the reasons
21 discussed above. Further, as discussed above, the Lovaza clinical trials showed that DHA

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23 ¹⁷⁸⁶ ATP-III at 3170; Bays 2008 I at 395.

24 ¹⁷⁸⁷ Kwiterovich in Kwiterovich at 4.

1 supplementation in very high TG patients *did not* increase Apo-B levels. A person of skill in the
2 art would have been aware of these data and accordingly would not have expected DHA therapy
3 to increase Apo-B levels in very high TG patients.

4 Defendants also do not even appear to assert that Kelley renders the asserted claim
5 obvious or identify a combination that includes Kelley. As a result, they necessarily fail explain
6 why there would be a motivation or reasonable expectation of success associated with a
7 combination that would include Kelley. To the extent that Defendants cite Kelley's disclosure to
8 suggest that EPA would have a different impact on lipid parameters than DHA, that argument is
9 incorrect. Kelley does not disclose the use of EPA. Further, Kelley, which was discussed above,
10 *see* Section VI, involved men with an average TG level of 226 mg/dL. A person of skill in the
11 art would not consider the results of Kelly in connection with forming an expectation regarding
12 the impact of EPA therapy on very high TG patients. Defendants fail to make even an assertion
13 to the contrary.

14 Accordingly, a person of ordinary skill in the art would not have been motivated to
15 administer the EPA composition to very high TG patients. For the same reasons, a person of
16 ordinary skill in the art would not have a reasonable expectation of success in achieving the
17 claimed invention.

18 (2) Dependent Claims

19 (a) Defendants Have Not Shown that Claims 2 and 6 of
20 the '335 Patent Would Have Been Obvious

21 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
22 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claim
23 by clear and convincing evidence, they also have not adequately proven the obviousness of
24 Claims 2 and 6.

1 Defendants contend, without support, that a person of ordinary skill would reasonably
2 expect that “a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL
3 synthesis.” Defendants further contend, without support, that it would have been obvious to a
4 person of ordinary skill to administer a composition containing EPA, but containing no DHA,
5 with a reasonable expectation of success in reducing Apo-B levels and thus also in reducing
6 LDL-C levels. Defendants conclude, without support, that there was a reasonable expectation of
7 success in reducing triglycerides while avoiding an increase in LDL without identifying any
8 combination of references and without explaining how each reference relates to the claimed
9 invention.¹⁷⁸⁸ These contentions: 1) do not assert what the prior art discloses to a person of
10 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
11 specific combination of claim elements were all present in the prior art references that would
12 have been combined by a person of ordinary skill in the art to produce the claimed invention
13 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.
14 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
15 reading the element out of the claim. Although convenient and expedient, Defendants’ approach
16 does not conform with the Local Patent Rules of this District, the law of claim construction, or
17 the law of obviousness.

18 Defendants do not identify any combination of references. Because Defendants do not
19 identify any combination of references, they necessarily fail to offer any evidence that a person
20 of skill in the art would be motivated to combine those references in order to achieve the
21

22 ¹⁷⁸⁸ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
23 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
24 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

1 invention of the claim as a whole. Defendants have not met their burden to establish *prima facie*
2 obviousness with the naked assertion that it would have been obvious to seek the claim element.

3 Similarly, without the disclosure of a combination of references and a motivation/reason
4 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
5 person of ordinary skill in the art would have had a reasonable expectation of success in
6 achieving the claimed invention. Defendants make a conclusory statement that there was a
7 reasonable expectation of success, without providing any support. As such, Defendants fail to
8 demonstrate reasonable expectation of success of the claimed invention.

9 (i) A Person of Ordinary Skill Would Not Have
10 Had a Reasonable Expectation of Success in
11 Replacing the Mixed Fish Oil Active
Ingredient in Lovaza with Pure EPA

12 Defendants provide no evidence that a person of ordinary skill would have had a
13 reasonable expectation of successfully obtaining the claimed invention—a method of reducing
14 triglycerides in a subject having very-high triglyceride levels by administering EPA of the
15 recited purity to effect a reduction in triglycerides *with the claimed LDL-C effect*—by combining
16 the references cited by defendants. For a particular combination of references, there must be a
17 reasonable expectation that the combination will produce the claimed invention. In this case, the
18 art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high
19 TG levels.¹⁷⁸⁹ A person of ordinary skill would have expected EPA, like Lovaza/Omacor, to
20 raise LDL-C levels when administered to patients in the very-high TG patient population. As

21
22 ¹⁷⁸⁹ As discussed above, see *supra* section III, a person of ordinary skill would have understood EPA and DHA to
23 have the same TG lowering mechanism and would have further understood that the increase in LDL-C
24 accompanying the TG-lowering effects of Lovaza was a product of that same mechanism. Accordingly, a person of
ordinary skill would have expected EPA to increase LDL-C levels in patients with very-high TG levels in similar
fashion to Lovaza or DHA alone.

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 ¹⁷⁹⁰	-20%	+45%
Lovaza/Omacor ¹⁷⁹¹	-6%	+45%

Accordingly, a person of ordinary skill would *not* have a reasonable expectation of success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with very-high TG levels.¹⁷⁹²

Defendants’ position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to patients with very high triglyceride levels to achieve TG lowering *with the claimed LDL-C effect* is belied by the fact that Defendants’ provide no evidence that anyone thought to administer Epadel.¹⁷⁹³ Epadel was available for many years prior to the invention of the ’335 patent, to patients with very-high TGs as a treatment. A person of ordinary skill did not expect Epadel, which consisted of mostly EPA,

¹⁷⁹⁰ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

¹⁷⁹¹ Chan 2002 I at 2381 (Table 3).

¹⁷⁹² 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.

¹⁷⁹³ Although Epadel was available at different levels of purity, the fact that Epadel—at any level of purity—was not examined in any study directed to the very-high TG patient population supports Amarin’s position.

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

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

13 Defendants argue that because Grimsgaard administered purified ethyl EPA to patients
14 with borderline-high/high TG, it would have been obvious to try administering purified ethyl
15 EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants
16 base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of
17 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.
18 Defendants' contentions are no more than a demonstration that certain claim elements was
19 known in the prior art and demonstrates impermissible hindsight reconstruction.¹⁷⁹⁴ As is
20 reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA,
21 EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA
22

23 ¹⁷⁹⁴ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under
24 KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention.”).

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

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

	DHA (n = 72)		EPA (n = 75)		Corn oil (n = 77)		F test: P ¹	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	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 ²	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 ²	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 ²	1.02 ± 0.28	0.02 ± 0.11	0.05	—	—	—
HDL:apolipoprotein A-I	0.97 ± 0.14	0.04 ± 0.07 ²	0.96 ± 0.13	0.04 ± 0.08 ²	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 ²	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 g ± 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.

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

5 Defendants argue that it would have been obvious to try administering purified ethyl EPA
6 to patients with very-high TG levels with a reasonable expectation of success. However, the
7 Federal Circuit has often rejected the notion that showing something may have been “obvious-to-
8 try” proves that the claimed invention was obvious where the prior art did not suggest what to
9 try.¹⁷⁹⁵ Rather than there being a limited number of options, the state of the art provided a
10 plethora of compositions and administration protocols associated with multiple kinds of TG-
11 lowering therapies.¹⁷⁹⁶ There were not a finite number of options for a person of ordinary skill
12 seeking to reduce TG levels without increasing LDL-C among the very-high TG patient
13 population.

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

23 ¹⁷⁹⁵ See *Sanofi*, 748 F.3d at 1360–61.

24 ¹⁷⁹⁶ See *supra* Section III.

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

7 (ii) A Person of Ordinary Skill Would Not Have
8 Had a Reasonable Expectation of Success in
9 Administering the Purified EPA in the
10 Dosing Regimen Recited in the Claims

10 Defendants contend that a “person of ordinary skill in the art would have been motivated
11 to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal
12 to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides.” Defendants
13 also argue that “[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would
14 have given a person of ordinary skill in the art a reasonable expectation of successfully
15 administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in
16 these subjects relative to baseline or placebo.” However, Defendants provide no evidence that a
17 person of ordinary skill would have had a reasonable expectation of success in a method of
18 reducing triglycerides in a subject having very-high triglyceride levels by administering purified
19 EPA to effect a reduction in triglycerides *with the claimed LDL-C effect*. Therefore, Defendants
20 fail to provide a reasonable expectation of success for the claimed invention.

21 Defendants further argue, that “because it was known that DHA and EPA were
22 comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have
23 reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified
24 EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been

1 obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition
 2 with a reasonable expectation of success that such administration would result in reducing
 3 triglycerides while avoiding an increase in LDL.” Defendants argument is without any basis. To
 4 the contrary, because a person of ordinary skill in the art would have understood DHA and EPA
 5 to lower TGs via the same mechanism, the person of ordinary skill in the art would have
 6 expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no
 7 explanation and cite to no article to support their argument that the similar effects on TG levels is
 8 a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on
 9 the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected
 10 both EPA and DHA, whether administered alone or in combination, would cause an increase in
 11 LDL-C when administered to the very high TG patient population.

12 The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients
 13 with very-high TG. A person of ordinary skill would have thus expected EPA, like
 14 Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient
 15 population. It was well known that TG-lowering agents, specifically fibrates and
 16 Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but
 17 caused significant increases in LDL-C levels for patients with very-high triglycerides. The art
 18 cited by Defendants provides no basis for a person of ordinary skill to expect anything to the
 19 contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including
 20 DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as
 21 reflected in the prior art:

	LDL-C Effect	
	Borderline-High or High TG Patients	Very-High TG Patients

Fibrate ¹⁷⁹⁷	-20%	+45%
Lovaza/Omacor ¹⁷⁹⁸	-6%	+45%

Accordingly, a person of ordinary skill would not have a reasonable expectation of success in achieving a reduction in TG levels *with the claimed LDL-C effect* in patients with very-high TG levels using EPA.

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administering purified EPA to the requisite patient population to achieve a lowering in TG levels *with the claimed LDL-C effect* 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 '335 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.

¹⁷⁹⁷ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

¹⁷⁹⁸ Chan 2002 I at 2381 (Table 3).

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

3 (b) Defendants Have Not Shown that Claims 3, 15, and
4 23 of the '335 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
6 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 3, 15 and 23.

9 Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach
10 the additional claim elements of dependent Claims 3, 15 and 15. Defendants contend, without
11 providing any support, that the claim elements are the results of simply optimizing the conditions
12 described in the prior art and within the purview of the skilled physicians. These contentions: 1)
13 do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant
14 to an obvious analysis; 3) fail to address whether the specific combination of claim elements
15 were all present in the prior art references that would have been combined by a person of
16 ordinary skill in the art to produce the claimed invention with a reasonable expectation of
17 success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious
18 analysis, but trivialize the claim element to the point of reading the element out of the claim.
19 Although convenient and expedient, Defendants' approach does not conform with the Local
20 Patent Rules of this District, the law of claim construction, or the law of obviousness.

21 Defendants fail to show a specific combination of references that discloses each element
22 of the claimed invention. None of the cited references discloses administration of the claimed
23 EPA to very high TG patients. Defendants further fail to explain how the cited references can be
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1 combined to teach the administration of the claimed EPA to very high TG patients.¹⁷⁹⁹
2 Defendants selectively cite to an unspecified, isolated disclosure within a reference without
3 considering other disclosures or even the reference as a whole. Each reference, however, must
4 be evaluated for all that it teaches.¹⁸⁰⁰ Defendants’ unsupported cobbling of selective disclosures
5 represents hindsight reconstruction.¹⁸⁰¹

6 Defendants fail to show a motivation or reason to combine or modify the references
7 recited above. Defendants make a conclusory statement that the claimed methods of treatment
8 “would have been obvious to one of ordinary skill in the art,” but such a naked assertion does not
9 show why a person of ordinary skill would have been motivated to combine the references to
10 achieve the claimed invention.¹⁸⁰²

11 Defendants fail to show a reasonable expectation that a person of ordinary skill would
12 have successfully achieved the claimed invention. In fact, other than simply identifying prior art
13 references that purportedly disclose disparate elements, Defendants do not even discuss whether
14 a person of ordinary skill would have expected that the combination to work for its intended
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18 ¹⁷⁹⁹ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

19 ¹⁸⁰⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

20 ¹⁸⁰¹ See, e.g., *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ¹⁸⁰² *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
23 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 purpose.¹⁸⁰³ As such, Defendants fail to demonstrate reasonable expectation of success of the
2 claimed invention.

3 (c) Defendants Have Not Shown that Claims 4, 16, and
4 24 of the '335 Patent Would Have Been Obvious

5 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
6 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims
7 by clear and convincing evidence, they also have not adequately proven the obviousness of
8 Claims 4, 16 and 24.

9 Defendants contend, without providing meaningful support, that the claim element was
10 well known in the art. These contentions: 1) do not assert what the prior art discloses to a
11 person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address
12 whether the specific combination of claim elements were all present in the prior art references
13 that would have been combined by a person of ordinary skill in the art to produce the claimed
14 invention with a reasonable expectation of success; and 4) fail to establish *prima facie*
15 obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the
16 point of reading the element out of the claim. Although convenient and expedient, Defendants'
17 approach does not conform with the Local Patent Rules of this District, the law of claim
18 construction, or the law of obviousness.

19 Defendants fail to show a specific combination of references that discloses each element
20 of the claimed invention. Defendants make a conclusory statement that the claimed method of
21 treatment was well known in the art, but such a naked assertion does not show why a person of

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23 ¹⁸⁰³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 ordinary skill would have been motivated to combine the references to achieve the claimed
2 invention.¹⁸⁰⁴ Further Defendants cite to the “Lovaza product” without identifying the prior art
3 reference to which they refer. Such a reference is inadequate.

4 Defendants fail to show a reasonable expectation that a person of ordinary skill would
5 have successfully achieved the claimed invention. Defendants do not even discuss whether a
6 person of ordinary skill would have expected that the combination to work for its intended
7 purpose.¹⁸⁰⁵ As such, Defendants fail to demonstrate reasonable expectation of success of the
8 claimed invention.

9 (d) Defendants Have Not Shown that Claims 5, 17, and
10 25 of the ‘335 Patent Would Have Been Obvious

11 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
12 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims
13 by clear and convincing evidence, they also have not adequately proven the obviousness of
14 Claims 5, 17 and 25.

15 Defendants do not identify any combination of references and simply provide a laundry
16 list of references without explaining how each reference relates to the claimed invention.
17 Defendants further contend, without any support, that a person of ordinary skill would have been
18 able to determine the patient population in need of the claimed methods of treatment, would seek

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20 ¹⁸⁰⁴*Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
21 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
22 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ¹⁸⁰⁵*DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat
2 those patients having very high triglycerides regardless of the baseline values of these lipids.¹⁸⁰⁶
3 These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in
4 the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific
5 combination of claim elements were all present in the prior art references that would have been
6 combined by a person of ordinary skill in the art to produce the claimed invention with a
7 reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants
8 do not offer an obvious analysis, but trivialize the claim element to the point of reading the
9 element out of the claim. Although convenient and expedient, Defendants' approach does not
10 conform with the Local Patent Rules of this District, the law of claim construction, or the law of
11 obviousness.

12 Defendants fail to show a specific combination of references that discloses each element
13 of the claimed invention. Defendants merely list references, without reference to a specific page
14 or section, that purportedly disclose disparate elements without explaining how they can be
15 combined.¹⁸⁰⁷ As such, Defendants discuss the claim elements in isolation, and fail to address
16 the claimed invention as a whole.¹⁸⁰⁸ Moreover, by simply identifying prior art references
17 without discussing the specific teachings of each reference, Defendants fail to consider each
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21 ¹⁸⁰⁶ *Id.*

22 ¹⁸⁰⁷ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art”).

23 ¹⁸⁰⁸ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim”).

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1 prior art reference as a whole.¹⁸⁰⁹ Each reference must be evaluated for all that it teaches.
2 Defendants’ unsupported cobbling of selective disclosures represents hindsight
3 reconstruction.¹⁸¹⁰

4 Because Defendants do not identify any combination of references, they necessarily fail
5 to offer any evidence that a person of skill in the art would be motivated to combine those
6 references in order to achieve the invention of the claim as a whole. Defendants make a
7 conclusory statement that a person of ordinary skill “would indeed seek” to perform the claimed
8 methods of treatment, without providing a reason that would have prompted a person of ordinary
9 skill to combine the elements.¹⁸¹¹ Such a naked assertion does not show why a person of
10 ordinary skill would have been motivated to treat the recited patient population using the claimed
11 methods of treatment.¹⁸¹²

12 Similarly, without the disclosure of a combination of references and a motivation/reason
13 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
14 person of ordinary skill in the art would have had a reasonable expectation of success in
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16 ¹⁸⁰⁹ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) (“A prior
17 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).

18 ¹⁸¹⁰ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
19 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

20 ¹⁸¹¹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
21 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted)

22 ¹⁸¹² *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
24 in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 achieving the claimed invention. In fact, other than simply identifying prior art references that
2 purportedly disclose disparate elements, Defendants do not even discuss whether a person of
3 ordinary skill would have expected that the combination to work for its intended purpose for
4 treating the recited patient population.¹⁸¹³ As such, Defendants fail to demonstrate reasonable
5 expectation of success of the claimed invention.

6 (e) Defendants Have Not Shown that Claims 7, 10, 19,
7 and 27 of the '335 Patent Would Have Been
8 Obvious

9 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
10 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims
11 by clear and convincing evidence, they also have not adequately proven the obviousness of
12 Claims 7, 10, 19 and 27.

13 Defendants contend it would have been obvious to use the claimed composition to reduce
14 VLDL-C levels. Defendants further contend that one of ordinary skill would “naturally seek to
15 reduce VLDL-C levels to a therapeutic level.” These contentions: 1) do not assert what the prior
16 art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3)
17 fail to address whether the specific combination of claim elements were all present in the prior
18 art references that would have been combined by a person of ordinary skill in the art to produce
19 the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima*
20 *facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element
21 to the point of reading the element out of the claim. Although convenient and expedient,
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23 ¹⁸¹³ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”)

1 Defendants' approach does not conform with the Local Patent Rules of this District, the law of
2 claim construction, or the law of obviousness.

3 Defendants do not identify any combination of references. Because Defendants do not
4 identify any combination of references, they necessarily fail to offer any evidence that a person
5 of skill in the art would be motivated to combine those references in order to achieve the
6 invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of
7 ordinary skill would have been motivated to combine the elements.¹⁸¹⁴ As such, Defendants fail
8 to demonstrate that there was no motivation to combine the references to achieve the claimed
9 invention.

10 Similarly, without the disclosure of a combination of references and a motivation/reason
11 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
12 person of ordinary skill in the art would have had a reasonable expectation of success in
13 achieving the claimed invention. Defendants do not even discuss the reasonable expectation of
14 reducing VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of
15 success of reducing VLDL-C levels using the claimed methods.

16 (f) Defendants Have Not Shown that Claims 8, 11, 20,
17 28 of the '335 Patent Would Have Been Obvious

18 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
19 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims
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21

22 ¹⁸¹⁴ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
23 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
24 the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

1 by clear and convincing evidence, they also have not adequately proven the obviousness of
2 Claims 8, 11, 20 and 28.

3 Defendants contend that EPA is known to reduce non-HDL-C and VLDL-C levels.
4 Defendants further contend that a person of ordinary skill would have a reasonable expectation
5 that a composition comprising EPA, but not DHA, would lower non-HDL-C levels, citing a
6 laundry list of references without explaining how each reference relates to the claimed
7 invention.¹⁸¹⁵ These contentions: 1) do not assert what the prior art discloses to a person of
8 ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the
9 specific combination of claim elements were all present in the prior art references that would
10 have been combined by a person of ordinary skill in the art to produce the claimed invention
11 with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness.
12 Defendants do not offer an obvious analysis, but trivialize the claim element to the point of
13 reading the element out of the claim. Although convenient and expedient, Defendants' approach
14 does not conform with the Local Patent Rules of this District, the law of claim construction, or
15 the law of obviousness.

16 Defendants do not identify any combination of references and simply provide a laundry
17 list of references that purportedly disclose disparate elements without explaining how they can
18 be combined.¹⁸¹⁶ As such, Defendants discuss the claim elements in isolation, and fail to address
19 the claimed invention as a whole.¹⁸¹⁷ Defendants selectively cite to an unspecified isolated

20 ¹⁸¹⁵ *Id.*

21 ¹⁸¹⁶ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v.*
22 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

23 ¹⁸¹⁷ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
24 made with respect to the subject matter as a whole, not separate pieces of the claim”).

1 disclosure within a reference without considering other disclosures or even the reference as a
2 whole. Each reference, however, must be evaluated for all that it teaches.¹⁸¹⁸ Defendants’
3 unsupported cobbling of selective disclosures represents hindsight reconstruction.¹⁸¹⁹

4 Because Defendants do not identify any combination of references, they necessarily fail
5 to offer any evidence that a person of skill in the art would be motivated to combine those
6 references in order to achieve the invention of the claim as a whole. In fact, Defendants do not
7 discuss at all whether a person of ordinary skill would have been motivated to combine the
8 elements.¹⁸²⁰ As such, Defendants fail to demonstrate that there was no motivation to combine
9 the references to achieve the claimed invention.

10 Similarly, without the disclosure of a combination of references and a motivation/reason
11 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
12 person of ordinary skill in the art would have had a reasonable expectation of success in
13 achieving the claimed invention. Defendants make a conclusory statement that a person of
14 ordinary skill “would have a reasonable expectation that a composition comprising EPA, but not
15 DHA would lower non-HDL-C levels,” without providing a support other than simply
16 identifying prior art references that purportedly disclose disparate elements.¹⁸²¹ The mere fact
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18 ¹⁸¹⁸ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

19 ¹⁸¹⁹ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
20 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

21 ¹⁸²⁰ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the *KSR*
22 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

23 ¹⁸²¹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
24 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

1 that elements are capable of being physically combined does not establish reasonable expectation
2 of success.¹⁸²² What is more, Defendants do not even discuss the reasonable expectation of
3 reducing non-HDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of
4 success of reducing non-HDL-C levels using the claimed methods.

5 (g) Defendants Have Not Shown that Claims 9, 12, 21,
6 and 29 of the '335 Patent Would Have Been
Obvious

7 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
8 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims
9 by clear and convincing evidence, they also have not adequately proven the obviousness of
10 Claims 9, 12, 21 and 29.

11 Defendants contend, without support, that a person of ordinary skill would naturally seek
12 to reduce total cholesterol level because it represents therapeutic efficacy. Defendants further
13 contend that recited percentage reductions of total cholesterol are obvious because there is no
14 significance regarding the percentage reductions. Defendants conclude, without support, that
15 there was a reasonable expectation of success without identifying any combination of references
16 and without explaining how each reference relates to the claimed invention. These contentions:

17 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are
18 irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim
19 elements were all present in the prior art references that would have been combined by a person
20 of ordinary skill in the art to produce the claimed invention with a reasonable expectation of

21 _____
22 underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

23 ¹⁸²² *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in *KSR* refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

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

5 Defendants do not identify any combination of references and simply provide a laundry
6 list of references that purportedly disclose disparate elements without explaining how they can
7 be combined.¹⁸²³ As such, Defendants discuss the claim elements in isolation, and fail to address
8 the claimed invention as a whole.¹⁸²⁴ Defendants selectively cite to an unspecified isolated
9 disclosure within a reference without considering other disclosures or even the reference as a
10 whole. Each reference, however, must be evaluated for all that it teaches.¹⁸²⁵ Defendants’
11 unsupported cobbling of selective disclosures represents hindsight reconstruction.¹⁸²⁶

12 Because Defendants do not identify any combination of references, they necessarily fail
13 to offer any evidence that a person of skill in the art would be motivated to combine those
14 references in order to achieve the invention of the claim as a whole. Defendants make a
15 conclusory statement that “it would have been obvious to the ordinarily skilled artisan to seek to
16 reduce total cholesterol by 5% to 15%,” without providing a reason that would have prompted a
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19 ¹⁸²³ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int’l Co. v.*
20 *Teleflex Inc.*, 550 U.S. 398, 418 (2007)) (“[A] patent composed of several elements is not proved obvious merely by
demonstrating that each of its elements was, independently, known in the prior art”).

21 ¹⁸²⁴ *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) (“The determination of obviousness is
made with respect to the subject matter as a whole, not separate pieces of the claim”).

22 ¹⁸²⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹⁸²⁶ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
24 *KSR*, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 person of ordinary skill to reduce total cholesterol by the recited amount.¹⁸²⁷ Defendants’ burden
2 to establish *prima facie* obviousness is not discharged because there is allegedly “no
3 significance” attached to the recited total cholesterol reduction amount.¹⁸²⁸ Defendants have not
4 met the burden with the naked assertion that it would have been obvious to seek the claimed
5 element.

6 Similarly, without the disclosure of a combination of references and a motivation/reason
7 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
8 person of ordinary skill in the art would have had a reasonable expectation of success in
9 achieving the claimed invention. Defendants make a conclusory statement that there was a
10 reasonable expectation of success, without providing a support other than merely identifying
11 prior art references that purportedly disclose disparate elements.¹⁸²⁹ The mere fact that elements
12 are capable of being physically combined does not establish reasonable expectation of
13 success.¹⁸³⁰

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17 ¹⁸²⁷ *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) (“While the KSR
18 Court rejected a rigid application of the teaching, suggestion, or motivation (‘TSM’) test in an obviousness inquiry,
the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill
in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness
determination.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

19 ¹⁸²⁸ Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been
20 established. See *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (“An applicant may overcome a *prima facie*
case of obviousness by establishing that the claimed range is critical . . .”) (internal quotation marks omitted).

21 ¹⁸²⁹ *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“Rejections on obviousness grounds cannot be
22 sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational
underpinning to support the legal conclusion of obviousness.”) (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir.
2006)) (internal quotation marks omitted).

23 ¹⁸³⁰ *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) (“[T]he ‘predictable
24 result’ discussed in KSR refers not only to the expectation that prior art elements are capable of being physically
combined, but also that the combination would have worked for its intended purpose.”).

1 (h) Defendants Have Not Shown that Claims 13 of the
2 '335 Patent Would Have Been Obvious

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

7 (i) Defendants Have Not Shown that Claims 18 and 26
8 of the '335 Patent Would Have Been Obvious

9 Plaintiffs incorporate by reference the discussion related to the Independent Claims in
10 Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claim
11 by clear and convincing evidence, they also have not adequately proven the obviousness of
12 Claims 18 and 26.

13 Defendants contend, without support, that a person of ordinary skill would reasonably
14 expect that “a pure EPA composition would effect a reduction in ApoB, as it was known to
15 reduce VLDL synthesis.” Defendants further contend, without support, that it would have been
16 obvious to a person of ordinary skill to “administer a composition containing EPA, but
17 containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus
18 also in reducing LDL-C levels.” Defendants conclude, without support, that there was a
19 reasonable expectation of success in “reducing ApoB levels and thus also in reducing LDL-C
20 levels” without identifying any combination of references and without explaining how each
21 reference relates to the claimed invention.¹⁸³¹ These contentions: 1) do not assert what the prior
22 art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3)

23 ¹⁸³¹ Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-
24 Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney
2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku,
von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

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

8 Defendants do not identify any combination of references. Because Defendants do not
9 identify any combination of references, they necessarily fail to offer any evidence that a person
10 of skill in the art would be motivated to combine those references in order to achieve the
11 invention of the claim as a whole. Defendants have not met their burden to establish *prima facie*
12 obviousness with the naked assertion that it would have been obvious to seek the claim element.

13 Similarly, without the disclosure of a combination of references and a motivation/reason
14 to combine or modify the references, Defendants necessarily fail to offer any evidence that a
15 person of ordinary skill in the art would have had a reasonable expectation of success in
16 achieving the claimed invention. Defendants make a conclusory statement that there was a
17 reasonable expectation of success, without providing any support. As such, Defendants fail to
18 demonstrate reasonable expectation of success of the claimed invention.

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1 **4. The '335 Patent is Not Invalid Under § 112**

2 a) Defendants Have Not Demonstrated that the Claims of the '335
3 Patent Are Invalid for Indefiniteness

4 35 U.S.C. ¶ 112(b) requires that a patentee “particularly point[] out and distinctly claim[]
5 the subject matter which the applicant regards as his invention.”¹⁸³² Patent claims are valid in
6 light of an indefiniteness challenge if they “inform, with reasonable certainty, those skilled in the
7 art about the scope of the invention” in light of the specification and the prosecution history.¹⁸³³
8 The Supreme Court has recognized that “absolute precision is unattainable” in claim language
9 and “the certainty which the law requires in patents is not greater than is reasonable.”¹⁸³⁴

10 Defendants further allege that the terms “4g per day of a pharmaceutical composition
11 comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate” and
12 “wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more
13 than about 0.6% by weight of all fatty acids combined” are indefinite. They contend that,
14 because there is no indication of how much of the pharmaceutical composition is composed of
15 fatty acids, by extension it is indefinite how much of each fatty acid is present in the
16 composition. This is incorrect. A claim can use a ratio to define amounts of components in a
17 product, using terms such as “percent by weight.”¹⁸³⁵ In light of the specification and

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19 ¹⁸³² Defendants were required to disclose the basis for their assertion of indefiniteness with respect to each term, and
20 they have not met that requirement. They simply make conclusory assertions regarding indefiniteness despite
21 bearing the burden of proof. Moreover, Defendants’ failure prevents Plaintiffs from responding to their assertions
22 other than by making conclusory assertions in return. Therefore, Defendants should be precluded from
23 supplementing their naked assertions with new basis in the course of the litigation.

24 ¹⁸³³ *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

¹⁸³⁴ *Id.* at 2129.

¹⁸³⁵ *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,

1 prosecution history, a person of ordinary skill would understand with reasonable certainty the
2 range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical
3 composition in relation to all fatty acids present.¹⁸³⁶ Therefore, these terms are not indefinite and
4 do not render the claims indefinite.

5 Defendants allege that a number of terms containing the phrases “about” and
6 “substantially” are indefinite. Defendants do not provide any reason why these terms are
7 indefinite other than that they contain the phrases “about” and “substantially.” But, of course,
8 these terms are routinely used in patent claims, and are not *per se* indefinite.¹⁸³⁷ In particular,
9 courts have held repeatedly that claims that contain the words “about” and “substantially” are not
10 indefinite.¹⁸³⁸ Here, a person of ordinary skill would understand with reasonable certainty what
11 is claimed when the claims are read in light of the specification and prosecution history.¹⁸³⁹

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14 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”).

15 ¹⁸³⁶ See generally the '335 patent and its prosecution history.

16 ¹⁸³⁷ *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.”).

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20 ¹⁸³⁸ 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 (. 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).

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23 ¹⁸³⁹ See generally the '335 patent and its prosecution history.

1 Therefore, the terms that contain the words “about” and “substantially” are not invalid for being
2 indefinite.

3 Defendants further allege that the term “who is not on a concomitant lipid altering
4 therapy” is indefinite. Defendants provide no basis for this allegation. In light of the
5 specification and the prosecution history, however, a person of ordinary skill in the art would
6 understand with reasonable certainty the scope of a “concomitant lipid altering therapy.”¹⁸⁴⁰
7 Moreover, lipid altering therapies are discussed in the patent specification.¹⁸⁴¹ Therefore, the
8 phrase “concomitant lipid altering therapy” does not render the claim indefinite.

9 Defendants further contend that the metes and bounds of the phrases “compared to
10 baseline” and “substantially no increase or a reduction in fasting LDL-C” are unclear.
11 Defendants do not provide the basis for the assertion other than stating that it is unclear and the
12 specification does not clarify its meaning. As discussed above, use of the phrase “substantially”
13 does not render a claim *per se* indefinite. In light of the specification and the prosecution
14 history, a person of ordinary skill in the art would know with reasonable certainty the scope of
15 the terms “compared to baseline” and “substantially no increase or a reduction in fasting LDL-C”
16 and therefore these terms do not render the claims indefinite.¹⁸⁴²

17 Defendants also allege that it is impossible to ascertain the metes and bounds of
18 “compared to a second subject [or control subject] having a fasting baseline triglyceride level of
19 500 mg/dl to about 2000 mg/dl.” A person of ordinary skill, however, would understand the
20 metes and bounds of the term in light of the specification and the prosecution history.¹⁸⁴³

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22 ¹⁸⁴⁰ See generally the '335 patent and its prosecution history.

23 ¹⁸⁴¹ See e.g., '335 patent at 12:43-46; 13:66-14:5.

24 ¹⁸⁴² See generally the '335 patent and its prosecution history.

¹⁸⁴³ See generally the '335 patent and its prosecution history.

1 Moreover, the method of comparing a subject to a second subject or control subject, such as a
2 placebo controlled, randomized, double blind study, would have been known to a person of
3 ordinary skill at the time of the invention. Therefore, the term does not render the claims
4 indefinite.

5 Finally, Defendants contend that the asserted claims improperly mix methods and
6 formulations because Plaintiffs' assertion of contributory infringement apparently suggests that
7 the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness
8 analysis is based on what the claim language informs a person of ordinary skill in the art in light
9 of the specification and the prosecution history. Defendants do not identify any actual claim
10 language that mixes methods and formulations. Moreover, contributory infringement may be
11 asserted and proven when a party sells "a material or apparatus for use in *practicing a patented*
12 *process . . . knowing the same to be especially made or especially adapted for use in an*
13 *infringement of such patent.*"¹⁸⁴⁴ Plaintiffs assert that Defendants' ANDA products will be used
14 in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound
15 itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are
16 mistaken and the '335 patent claims are not indefinite for improperly mixing methods and
17 formulations.

18 b) Defendants Have Not Demonstrated that the Claims of the '335
19 Patent Are Invalid for Insufficient Written Description

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

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24 ¹⁸⁴⁴ 35 U.S.C. § 271(c) (emphasis added).

1 application was filed.¹⁸⁴⁵ Support need not be literal¹⁸⁴⁶—it may be implicit¹⁸⁴⁷ or inherent¹⁸⁴⁸ in
2 the disclosure. In addition, it is unnecessary to include information that is already known or
3 available to persons of ordinary skill.¹⁸⁴⁹

4 Defendants make three arguments regarding the written description requirement. First,
5 Defendants contend that elements reciting the baseline TG levels of the asserted claims lack
6 written description. This is incorrect. The specification of asserted patents literally discloses the
7 claimed invention.¹⁸⁵⁰ Defendants do not contend that the patient population of the asserted
8 claims is not literally described by the specification. In fact, the specification at the time of filing
9 described these limitations. Therefore, Defendants have failed to explain whether and how an
10 aspect of the claimed invention has not been described with sufficient particularity such that one
11 skilled in the art would recognize that the applicant had possession of the claimed invention.

12 Second, Defendants contend that “a person of skill in the art would not understand that
13 the inventor was in possession of a method incorporating [] specific dosages and quantities.”
14 Defendants’ assertion is incorrect. The specification of the asserted patents literally discloses the
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17 ¹⁸⁴⁵ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

18 ¹⁸⁴⁶ *Id.* at 1352; *Cordis Corp. v. Medtronic AVE, Inc.*, 339 F.3d 1352, 1365 (Fed. Cir. 2003); *In re Wright*, 866 F.2d
422, 425 (Fed. Cir. 1989); *In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973).

19 ¹⁸⁴⁷ *All Dental Prodx, LLC v. Advantage Dental Prods. Inc.*, 309 F.3d 774, 779 (Fed. Cir. 2002); *In re Wright*, 866
F.2d at 424–25.

20 ¹⁸⁴⁸ *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

21 ¹⁸⁴⁹ *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1367–68 (Fed. Cir. 2006); *Capon v. Eshhar*, 418 F.3d 1349,
1357 (Fed. Cir. 2005); *In re Gay*, 309 F.2d at 774.

22 ¹⁸⁵⁰ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
23 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
24 legal foundation for claiming that species.”).

1 dosages and quantities of the claimed methods.¹⁸⁵¹ Moreover, the dosages and quantities of the
2 method appear in the claims, as originally filed. Thus, there is a strong presumption that the
3 claimed invention is adequately described.¹⁸⁵² Defendants do not and cannot rebut this
4 presumption. For example, the dosage of the composition was originally claimed as “about 1 g
5 to about 4g.”¹⁸⁵³ The asserted claims recite “4 g.” Defendants do not contend that dosages and
6 quantities of the asserted claims are not literally described by the specification and in the original
7 claims. In fact, the specification and the provisional patent application claims, at the time of
8 filing, described these limitations. Therefore, Defendants have failed to explain whether and
9 how an aspect of the claimed invention has not been described with sufficient particularity such
10 that one skilled in the art would recognize that the applicant had possession of the claimed
11 invention.

12 Third, Defendants contend that a person of skill in the art would not understand that the
13 inventor was in possession of a method comprising a comparison against a ‘baseline’ or a second
14 subject. Although this allegation does not appear to implicate written description, the
15 specification describes that the applicants were in possession of the claimed inventions. For
16 example, a person of ordinary skill would have understood that the inventor was in possession of
17 a method comprising administration of a composition with the recited properties, based on a
18 comparison against a baseline or a second subject.

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20 ¹⁸⁵¹ *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (“[T]he test requires an objective
21 inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.”);
Snitzer v. Etzel, 465 F.2d 899, 902 (C.C.P.A. 1972) (“[T]he literal description of a species provides the requisite
22 legal foundation for claiming that species.”).

23 ¹⁸⁵² *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976) (“we are of the opinion that the PTO has the
24 initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure
a description of the invention defined by the claims”).

¹⁸⁵³ See U.S. Provisional Application No. 61/151,291.

1 In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,¹⁸⁵⁴ the court
2 elaborated that “possession” means possession as evidenced by disclosure. In this case, the
3 specification of asserted patents literally disclose the claimed invention in the specification and
4 the claims as originally filed. Thus, an examination of the four corners of the specification from
5 the perspective of a person of ordinary skill in the art demonstrates that the inventors of the
6 asserted patents were in possession of the claimed invention.

7 Defendants conclude by alleging that the specification does not describe anything more
8 than what is obvious, and thus does not provide adequate support for any nonobvious claim.
9 That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the
10 specification; nonobviousness can be supported by post-filing date evidence for example.¹⁸⁵⁵
11 Written description requires only that the specification reasonably conveys that the applicant had
12 possession of the claimed subject matter when the application was filed. Therefore, whether the
13 claims are obvious has no bearing on the adequacy of written description.

14 c) Defendants Have Not Demonstrated that the Claims of the ‘335
15 Patent Are Invalid for Lack of Enablement

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

19 ¹⁸⁵⁴ *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

20 ¹⁸⁵⁵ See *Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014)
21 (“Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is
22 incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those
23 characteristics become manifest.”); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291,
24 1307 (. 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 (. 2004) (“Evidence
developed after the patent grant is not excluded from consideration, for understanding of the full range of an
invention is not always achieved at the time of filing the patent application.”).

1 Factors that may be considered include the quantity of experimentation necessary, the amount of
2 direction or guidance presented, the presence or absence of working examples, the nature of the
3 invention, the state of the prior art, the relative skill of those in the art, the predictability or
4 unpredictability of the art, and the breadth of the claims.¹⁸⁵⁶ The enablement requirement is
5 separate and distinct from the written description requirement,¹⁸⁵⁷ and as such a claim does not
6 require descriptive support in the disclosure as originally filed for it to be enabled.¹⁸⁵⁸

7 Defendants make two specific arguments regarding the enablement requirement. First,
8 Defendants contend that “[i]t would take undue experimentation to obtain the actual amounts of
9 the composition found in the ultimate claims.” This is incorrect. As Defendants admit, the
10 claims disclose amounts of the composition to be administered. Therefore, a person of ordinary
11 skill would be able to determine the amounts of the components in the pharmaceutical
12 composition without any experimentation, much less undue experimentation.

13 Second, Defendants contend that it would take undue experimentation to obtain the
14 claimed required results listed in the full scope of the patent claims, including the claimed lipid
15 effects. This is incorrect. The asserted claims require no experimentation to practice the claimed
16 method and certainly not undue experimentation. Administration of a recited amount of a recited
17 composition, for a recited duration, to a specific, recited patient population produces the recited
18 results. No additional experimentation is required, and Defendants do not explain their
19 allegation that undue experimentation would be required. Defendants also do not contend that
20 following the claimed method (each recited element) does not produce the recited results. The
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22 ¹⁸⁵⁶ See, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

23 ¹⁸⁵⁷ *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

24 ¹⁸⁵⁸ MPEP § 2164.

1 clinical studies included in the VASCEPA® label and submitted to the USPTO clearly
2 demonstrate that administration of EPA of the recited composition, when administered to
3 patients with very high TG levels for at least 12 weeks, as specified, produces the recited
4 results.¹⁸⁵⁹ Therefore, the claims are not invalid for lack of enablement.

5 Defendants conclude by alleging that the specification does not enable anything more
6 than what is obvious over the prior art or was known to a person of skill in the art. First,
7 Defendants do not cite any case or present a legal theory to support this assertion. As such, they
8 do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be
9 precluded in the future from raising any new legal theory to support this assertion. Moreover,
10 while the '335 patent's specification enables a person of ordinary skill to obtain the claimed
11 limitations without undue experiment, the claimed limitations would not have been obvious to a
12 person of ordinary skill, as discussed in Section V.C.3. Furthermore, Plaintiffs have initiated
13 human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its
14 claimed methods.^{1860, 1861} Therefore, a person of ordinary skill would have concluded that the
15 claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

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21 ¹⁸⁵⁹ See VASCEPA Prescribing Information at Table 2.

22 ¹⁸⁶⁰ *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence “can be used to substantiate any
23 doubts as to the asserted utility.”); MPEP § 2107.03 (“[A]s a general rule, if an applicant has initiated human clinical
24 trials for a therapeutic product or process, Office personnel should presume that the applicant has established that
the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.”).

¹⁸⁶¹ See May 16, 2011 Bays Declaration at Appendix B.

1 D. **The '399 Patent**

2 **1. The '399 Patent Claims Eligible Subject Matter Under § 101**

3 Defendants' allegation that the asserted claims of the '399 patent relate to ineligible
4 subject matter under Section 101 is without merit. Defendants do not establish a *prima facie*
5 case under Section 101 or provide a legal or factual basis to support their allegations.

6 As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local
7 Patent Rules as the grounds for any allegation of invalidity under Section 101 must be
8 provided.¹⁸⁶² The bare assertion of invalidity under Section 101 without providing the grounds
9 for such an allegation and examining the elements of the asserted claims of the '399 patent does
10 not meet this requirement and thwarts the purpose of the Rules.¹⁸⁶³

11 The inquiry under Section 101 involves a two-step test: first, a court must determine
12 whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical
13 phenomenon, or abstract idea.¹⁸⁶⁴ Second, even if the claim is directed to one of these concepts,
14 it still may be patent eligible and the court must determine what else is part of the claim.¹⁸⁶⁵

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17 ¹⁸⁶² See Nevada Local Patent Rule 1.8(e) (“[E]ach party opposing a claim of patent infringement, shall serve on all
18 other parties Non-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed
statement of any grounds of invalidity based on 35 U.S.C. § 101.”).

19 ¹⁸⁶³ Nor does the preceding paragraph, which provides only a purported summary of the claims of the '399 patent, or
20 subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the
21 grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. See, e.g., *Silver State Intellectual Techs.,
Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) (“The District of Nevada’s Local Patent
Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide
early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those
contentions when new information comes to light in the course of discovery”) (internal quotation marks omitted).

22 ¹⁸⁶⁴ *Alice Corp. Pty. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2355 (2014) (“First, we determine whether the claims at
23 issue are directed to one of those patent-ineligible concepts.”).

24 ¹⁸⁶⁵ *Id.* (quoting *Mayo*, 132 S. Ct. at 1294) (“If so, we then ask, ‘[w]hat else is there in the claims before us?’”).

1 The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v.*
2 *Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of
3 the '399 patent. In *Mayo*, the claims were directed to “well-understood, routine, [and]
4 conventional” steps, and the only novel element related to administering the proper dosage based
5 on a natural law observation.¹⁸⁶⁶ However, the claims merely recited this natural law without
6 reciting any novel application of it.¹⁸⁶⁷ The Court found that providing protection to such
7 claims would result in pre-empting “a broad range of potential uses” and excluding others from
8 using “the basic tools of scientific and technical work.”¹⁸⁶⁸ A method of treatment claim,
9 specifying the subjects, dosage levels, composition, and time course does not raise the concerns
10 of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent
11 protection.¹⁸⁶⁹

12 Defendants suggest that the recited EPA composition of each asserted claim is a naturally
13 occurring substance. It is not. Even references contained within Defendants’ own contentions
14 make clear that EPA of the requisite purity and characteristics is not found in nature.¹⁸⁷⁰ As
15 expressed by the patents cited in Defendants’ contentions and well-established precedent, for
16 decades it has been accepted that compositions isolated from nature or purified beyond their

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18 ¹⁸⁶⁶ *Mayo*, 132 S. Ct. at 1294.

19 ¹⁸⁶⁷ *Id.* at 1301.

20 ¹⁸⁶⁸ *Id.*

21 ¹⁸⁶⁹ *Id.* at 1302 (contrasting the patent-ineligible claims of that case to “a typical patent on a new drug or a new way
22 of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177 , 191-193 (1981) (upholding patentability
23 for “a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula
24 and a programmed digital computer” under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d
1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent
eligible claims, such as method of treatment claims, would also be necessarily ineligible).

¹⁸⁷⁰ *See, e.g.*, U.S. Patent No. 5,215,630, “Method of Purifying Eicosapentaenoic Acid or the Ester Derivative
Thereof by Fractional Distillation” (cited in Defendants’ Joint Invalidity Contentions, *e.g.*, at 26–27).

1 natural state are patent-eligible.¹⁸⁷¹ Moreover, Defendants’ assertions are immaterial to a Section
2 101 defense because method of treatment claims like the ones asserted in this case are patent
3 eligible even if they are directed to administration of a naturally occurring substance.¹⁸⁷²

4 To the extent Defendants are arguing that a law of nature both underlies the claims and
5 renders them ineligible, that argument is unsupported and incorrect. Defendants allege that “the
6 claimed effects are the natural result of ingesting a naturally-occurring substance.”¹⁸⁷³ Since the
7 composition that is the subject of the claims is not naturally occurring, Defendants appear to
8 suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states
9 or even suggests, and indeed the Federal Circuit has refused to adopt Defendants’ overbroad
10 characterization of laws of nature.¹⁸⁷⁴ To say that the claims of the ’399 patent claim a law of
11 nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode
12 of analysis that the Supreme Court did not adopt in which “all inventions can be reduced to
13 underlying principles of nature” that would “make all inventions unpatentable.”¹⁸⁷⁵ Indeed, even
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18 ¹⁸⁷¹ See, e.g., *In re Bergy*, 596 F.2d 952; *In re Kratz*, 592 F.2d 1169 (CCPA 1979); *In re Bergstrom*, 427 F.2d 1394
(CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

19 ¹⁸⁷² *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

20 ¹⁸⁷³ See Defendants’ Joint Invalidity Contentions at 522.

21 ¹⁸⁷⁴ See *CellzDirect*, 827 F.3d at 1048-49 (“The [asserted] claims are like thousands of others that recite processes
22 to achieve a desired outcome That one way of describing the process is to describe the natural ability of the
subject matter to *undergo* the process does not make the claim ‘directed to’ that natural ability. If that were so, we
would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells’ inability
to survive chemotherapy), or treating headaches with aspirin (as directed to the human body’s natural response to
aspirin).”).

23 ¹⁸⁷⁵ See *Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).
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1 those concerned about the implications of *Mayo* on future patents were focused on diagnostic
2 claims not treatment claims of the type that *Mayo* stated were typical and patentable.¹⁸⁷⁶

3 Even if there is some underlying law of nature in the asserted claims, the subject matter
4 of the '399 patent remains eligible for protection under Section 101. As articulated by *Mayo* and
5 *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to
6 protection where claims “did not ‘seek to pre-empt the use of [the] equation,’ but sought ‘only to
7 foreclose from others the use of that equation in conjunction with all of the other steps in their
8 claimed process.’”¹⁸⁷⁷ As discussed above, the asserted claims of the '399 patent contain a
9 novel, unconventional, and specific method of treatment comprising a particularized application
10 of a nonnaturally occurring substance and does not preempt the use of a law of nature.¹⁸⁷⁸

11 Defendants also argue that any argument by Amarin in response to Defendants’ § 112
12 arguments are further evidence of invalidity under § 101. This argument is without merit. The
13 claims are enabled and written description is satisfied for the reasons discussed below. In
14 addition, as discussed above, the asserted claims are not merely a naturally-occurring
15 phenomena, and thus satisfy the requirements of § 101.

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20 ¹⁸⁷⁶ See *Mayo*, 132 S. Ct. at 1034 (“Prometheus, supported by several *amici*, argues that a principle of law denying
21 patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries,
particularly in the area of diagnostic research.”).

22 ¹⁸⁷⁷ See *Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

23 ¹⁸⁷⁸ See, e.g., *Tannas Electronics v. Luxell Technologies, Inc.*, 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012)
24 (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was
“just one step in the whole process” claimed by the invention).

1 **2. The Asserted Claims of the ‘399 Patent Are Not Anticipated by WO**
2 **‘118**

3 To anticipate, a single prior art reference must sufficiently describe a claimed invention
4 so that the public is in “possession” of that invention.¹⁸⁷⁹ Therefore, to anticipate, a reference
5 must set forth every element of the claim, either expressly or inherently, in as complete detail as
6 is contained in the claim.¹⁸⁸⁰ The claim elements must also be “arranged” in the prior art
7 reference, just as they are in the claim,¹⁸⁸¹ rather than as “multiple, distinct teachings that the
8 artisan might somehow combine to achieve the claimed invention.”¹⁸⁸² In addition, public
9 “possession” requires that the prior art enable a person of ordinary skill to make and use the
10 invention without undue experimentation.¹⁸⁸³ Factors that may be included in this analysis
11 include the quantity of experimentation necessary, the amount of direction or guidance
12 presented, the presence or absence of working examples, the nature of the invention, the state of
13 the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,
14 and the breadth of the claims.¹⁸⁸⁴ This inquiry is objective, and thus evidence of undue
15 experimentation need not be prior art.¹⁸⁸⁵

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¹⁸⁷⁹ *Akzo N.V. v. U.S. Int’l Trade Com’n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

17 ¹⁸⁸⁰ *Id.*; *In re Bond*, 910 F.2d 831, 832 (Fed. Cir. 1990); *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed.
18 Cir. 1989).

¹⁸⁸¹ *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

19 ¹⁸⁸² *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369–71 (Fed. Cir. 2008); *In re Arkley*, 455 F.2d 586, 587
20 (C.C.P.A. 1972); *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965).

¹⁸⁸³ *Akzo*, 808 F.2d at 1479; *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1085 (Fed. Cir. 2008); *Forest Labs.,
21 Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1268–69 (Fed. Cir. 2007).

¹⁸⁸⁴ *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

22 ¹⁸⁸⁵ *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999
23 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc.*, 449 F.3d 1209, 1224–25 (Fed. Cir.
24 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822
F.2d 1074, 1078 (Fed. Cir. 1987).

1 Defendants assert that Claims 1-9 of the '399 Patent are anticipated by the WO '118
2 reference.¹⁸⁸⁶

3 A element-by-element analysis, identifying each element of each asserted claim that is
4 absent from WO '118, is provided below. The contentions below are incorporated by reference
5 into Exhibit D, and vice-versa. WO '118 does not anticipate the claims of the '399 patent
6 because it does not describe, properly arrange, or enable the '399 patent claims.

7 a) WO '118 Does Not Teach Every Element of the Claims of the
8 '399 Patent

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

10 It is well established that, for a prior art reference to anticipate, “every element of the
11 claimed invention must be identically shown in a single reference.”¹⁸⁸⁷ Moreover, the elements
12 of the claimed invention must have “strict identity” with the elements of the reference; “minimal
13 and obvious” differences are sufficient to prevent anticipation.¹⁸⁸⁸ Here, WO '118 entirely fails
14 to disclose the following elements of Claim 1 of the '399 Patent: *to effect a reduction in*
15 *triglycerides without substantially increasing LDL-C compared to a second group of subjects*
16 *having a median fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who have*
17 *not received the pharmaceutical composition and a concurrent lipid altering therapy.*

18 Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail
19 to set forth any basis for concluding that WO '118 teaches this element.¹⁸⁸⁹ Indeed, Defendants

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21 ¹⁸⁸⁶ References to “WO '118” are to the English translation that was filed with the European application. Plaintiffs reserve their right to obtain a certified translation of WO '118.

22 ¹⁸⁸⁷ *Diversitech Corp. v. Century Steps, Inc.*, 850 F.2d 675, 677 (Fed. Cir. 1988); *see also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986).

23 ¹⁸⁸⁸ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

24 ¹⁸⁸⁹ Defendants' Invalidation Contentions at 202-204.

1 could not set forth any basis for concluding that WO ‘118 teaches this element because WO ‘118
2 does not.

3 Instead, Defendants argue that these elements express the intended result of a method that
4 is positively recited, and therefore is inherently anticipated. However, for the reasons set forth
5 below, WO ‘118 fails to disclose each element of the independent claim of the ‘399 Patent, either
6 expressly or inherently. Therefore, WO ‘118 cannot anticipate the claimed method. Defendants
7 also argue that these elements represent inherent, natural properties of EPA, and are entitled to
8 no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation
9 and claim construction. Further, while Defendants argue that the inherent properties are
10 exemplified in the prior art, they fail to identify even a single prior art reference that makes such
11 a disclosure. Defendants cannot point to a single, specific prior art reference because the
12 claimed pharmaceutical composition has never been administered in the manner claimed to the
13 claimed patient population. Also, these elements are positively recited in the body of the claim
14 and therefore cannot be construed as a non-limiting preamble and must be given patentable
15 weight.

16 Further, Defendants entirely fail to prove that inherently discloses the claimed lipid
17 effects. A prior art reference that “only ‘probably’ or ‘possibly’ meets the claims cannot
18 inherently anticipate as a matter of law.”¹⁸⁹⁰ “[A]nticipation by inherent disclosure is appropriate
19 only when the reference discloses prior art that must *necessarily* include the unstated
20 limitation.”¹⁸⁹¹ “It is not sufficient if a material element or limitation is ‘merely probably or
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23 ¹⁸⁹⁰ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

24 ¹⁸⁹¹ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

1 possibly present' in the prior art.”¹⁸⁹² WO ‘118 fails to provide any data related to the lipid
2 effects of the disclosed invention on patients described in the publication. Therefore, Defendants
3 fail to prove by clear and convincing evidence that the composition disclosed by WO ‘118 meets
4 the elements of the independent claim every time it is administered.

5 Defendants fail to demonstrate that administration of the claimed EPA compositions
6 “necessarily” yields the claimed lipid effects. For example, one study cited by Defendants
7 suggests that EPA administration may increase LDL-C.¹⁸⁹³ Rambjor is a clinical study which
8 administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA
9 and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a
10 non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not*
11 decrease TG without increasing LDL-C *every time it is administered*.

12 Therefore, WO ‘118 cannot anticipate the independent claim of the ‘399 patent. Because
13 the dependent claims include all of the claim elements of the independent claim, WO’ 118
14 cannot anticipate any of the dependent claims as well.

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

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

23 ¹⁸⁹² *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 ¹⁸⁹³ *See, e.g., Rambjor.*

1 A claim preamble has patentable weight if, “when read in the context of the entire claim,
2 [it] recites limitations of the claim, or, if the claim preamble is ‘necessary to give life, meaning,
3 and vitality’ to the claim.”¹⁸⁹⁴ Additionally, the preamble constitutes a claim element when the
4 claim depends on it for antecedent basis because “it indicates reliance on both the preamble and
5 claim body to define the claimed limitation.”¹⁸⁹⁵

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

10 If the preamble states “a fundamental characteristic of the claimed invention,” then it “is
11 properly construed as a limitation of the claim itself.”¹⁸⁹⁶ The recitation of a “method of
12 reducing triglycerides” in the preamble provides antecedent basis for the effect of reducing
13 triglycerides in the body of the claim and emphasizes the intentional purpose for which the
14 method must be performed - to reduce triglycerides.

15 It is clear that “the claim drafter chose to use both the preamble and the body of the claim
16 to define the subject matter of the claimed invention.”¹⁸⁹⁷ Thus, the entire preamble in the
17 independent claim of the ‘399 must contain patentable weight.

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20 ¹⁸⁹⁴ *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

21 ¹⁸⁹⁵ *Catalina Marketing Int’l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

22 ¹⁸⁹⁶ *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cir. 2004); *see also e.g., Computer*
Docking Station Corp. v. Dell, Inc., 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases
23 “portable computer” and “portable computer microprocessing system” limit the claims because they “clearly recite a
necessary and defining aspect of the invention, specifically its portability,” and because the specification and
prosecution history “emphasize this feature of the invention”).

24 ¹⁸⁹⁷ *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

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

4 First, WO '118 fails to expressly disclose “a method of reducing triglycerides.” In fact,
5 the invention disclosed by WO '118 relates to a composition for **preventing occurrence of**
6 **cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the
7 Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence
8 of cardiovascular events is defined in WO '118 as “all cases of primary prevention, and
9 exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden
10 cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest
11 angina and exercise-induced angina, and destabilization of the angina.”¹⁸⁹⁸ The invention of WO
12 '118 is intended to be administered to any person in need of prevention of the occurrence of
13 cardiovascular events, who are typically hypercholesterolemia patients.¹⁸⁹⁹ WO '118 does not
14 expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot
15 anticipate the independent claim.

16 Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail
17 to prove that these elements of the claimed invention have “strict identity” with the elements of
18 the reference.¹⁹⁰⁰ WO '118 fails to anticipate this claim element because the broad disclosure
19 fails to anticipate the narrow claimed range, and the specific patient population defined in the
20 claims is an essential part of the claimed invention.

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¹⁸⁹⁸ WO '118 at 12.

23 ¹⁸⁹⁹ *Id.*

24 ¹⁹⁰⁰ *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

1 There is no evidence in that subject as described in the claims were ever treated. In fact,
2 WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the
3 definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of
4 the subject as described in the claims. It does not. Defendants' argument rests on the definition
5 in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150
6 mg/dL." WO '118's definition is not tied to a specific subject and there are no working
7 examples, data or other reference in WO '118 indicating that any subject with fasting TG levels
8 of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any
9 EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as
10 evidence that a "person of ordinary skill in the art would have understood that the term
11 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of
12 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable
13 and then merely provides examples of commercially available "soft capsules," such as Omacor.
14 The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients
15 with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be
16 used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably'
17 or 'possibly' meets the claims cannot inherently anticipate as a matter of law."¹⁹⁰¹ Therefore,
18 Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO
19 '118 meets the claim elements of the independent claim every time it is administered.

20 Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges
21 claimed by the '399 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500
22 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between
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24 ¹⁹⁰¹ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

1 330 and 450 degrees. The court found that the broader prior art range could not anticipate the
2 claimed temperature range, “[g]iven the considerable difference between the claimed range and
3 the range in the prior art, no reasonable fact finder could conclude that the prior art describes the
4 claimed range with sufficient specificity to anticipate this element of the claim.”¹⁹⁰² A prior art’s
5 teaching of a broad genus does not necessarily disclose every species within that genus. The
6 court explained the slightly overlapping range between the preferred range and claimed range “is
7 not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”¹⁹⁰³ and therefore
8 failed to anticipate the claimed range. Likewise, WO ‘118’s broad disclosure of
9 hypertriglyceridemia as a “fasting serum triglyceride levels of at least 150 mg/dL” does not
10 anticipate the subject as described in the claims because it fails to described the claimed TG
11 range with sufficient specificity.

12 The court in *Atofina* ruled on an additional question of anticipation that also involved a
13 range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as
14 compared to the patent’s claimed range of 0.1 to 5.0 percent.¹⁹⁰⁴ The court explained that
15 “although there is a slight overlap, no reasonable fact finder could determine that this overlap
16 describes the entire claimed range with sufficient specificity to anticipate this limitation of the
17 claim. The ranges are different, not the same. . . . Thus, there is no anticipation.”¹⁹⁰⁵ Similarly,
18 although there may be overlap between the definition of hypertriglyceridemia taught by WO
19 ‘118 and the TG range recited by the claims of the asserted patents, WO ‘118 does not
20 specifically discuss, highlight or otherwise suggest treating patients with TG values above 500

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22 ¹⁹⁰² *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

23 ¹⁹⁰³ *Atofina*, 441 F.3d at 1000.

24 ¹⁹⁰⁴ *Id.*

¹⁹⁰⁵ *Id.*

1 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of
2 cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels
3 below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic
4 events as the primary clinical objective),¹⁹⁰⁶ WO '118, therefore, does not expressly disclose the
5 specific patient population that is an essential element of the claims of the asserted patents.
6 Therefore, WO '118 cannot anticipate the claims of the asserted patents.

7 The treatment of a patient with elevated TG levels varies depending on their serum
8 triglyceride levels. Identification of the patient population with very high TG levels (at least 500
9 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders,
10 including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment
11 of lipid disorders.¹⁹⁰⁷ The ATP-III divided hypertriglyceridemia patients into three classes based
12 on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),
13 and very-high TGs (\geq 500 mg/dL)—and recommended substantially different treatment
14 strategies for patients depending on classification.¹⁹⁰⁸ For the borderline-high and high TG
15 groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.¹⁹⁰⁹
16 Accordingly, in these populations, physicians focused on lowering LDL-C.¹⁹¹⁰ In this patient
17 population, lowering of TG and non-HDL-C levels were considered secondary treatment goals.
18 In contrast, the primary goal for very-high TG patients (\geq 500 mg/dL) was to reduce the risk of
19 pancreatitis—a potentially life threatening condition expected to be precipitated by elevated

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21 ¹⁹⁰⁶ See Section III.

22 ¹⁹⁰⁷ *Id.*

23 ¹⁹⁰⁸ ATP III at 3335; *See also* Section III.

24 ¹⁹⁰⁹ *Id.*

¹⁹¹⁰ *Id.*

1 TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary
2 treatment goal.¹⁹¹¹ Therefore, as evidenced by the ATP-III, patients with very-high TG levels
3 were considered fundamentally different from patients with borderline-high or high TGs from a
4 lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

5 Therefore, WO ‘118’s definition of “hypertriglyceridemia” as “fasting serum triglyceride
6 levels of at least 150 mg/dL” fails to anticipate the claimed subject with very high TG levels. In
7 fact, as described above, WO ‘118 is not directed toward patients with the claimed TG levels at
8 all. WO 118’s disclosure is clearly directed towards preventing the occurrence of cardiovascular
9 risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL).
10 Thus, WO ‘118’s disclosure is *not* directed towards patients with very high triglyceride levels
11 (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by
12 decreasing triglycerides), as required by the independent claims of the asserted patents, and
13 therefore cannot anticipate the independent claim of the ‘399 Patent.

14 Third, WO ‘118 fails to disclose the claim element of “a second group of subjects . . .
15 who have not received the pharmaceutical composition and a concurrent lipid altering therapy.”
16 Defendants’ only basis for concluding that WO ‘118 teaches this element is that WO ‘118
17 “discloses and claims the administration of EPA-E without the administration in combination
18 with statins.”¹⁹¹² This sentence appears to be incomplete, as it is unclear what Defendants mean
19 by “without the administration in combination with statins.” This single statement, without
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22 ¹⁹¹¹ *Id.*

23 ¹⁹¹² Defendants’ Invalidity Contentions at 46.

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1 citation to a single page in WO '118, fails to demonstrate that WO '118 teaches this element. In
2 fact, WO '118 methods comprise statins, i.e. HMG-CoA RI.¹⁹¹³

3 WO '118 states that its disclosed composition is “effective in preventing occurrence of
4 cardiovascular events in hypercholesterolemia patients, and **in particular**, in preventing
5 occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with
6 HMG-CoA RI but still suffer from the risk of the cardiovascular events.”¹⁹¹⁴ WO '118 goes on
7 to state that the “effect of the composition of the present invention will be synergistically
8 improved by combined use with the HMG-CoA RI, and such use of the composition of the
9 present invention with the HMG-CoA RI has clinical utility since the effect of preventing the
10 cardiovascular event occurrence is expected to be improved.”¹⁹¹⁵ Administering the composition
11 of WO '118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-
12 CoA RI has on the disclosed compound. Further, WO '118 teaches that the disclosed
13 composition may be used with a long list of other drugs, including lipid altering drugs such as
14 antilipotropic drugs and fibrate drugs.¹⁹¹⁶ Thus, WO '118 does not disclose administration of the
15 claimed EPA compositions to a subject that has very high TG levels and also “a second group of
16 subjects . . . who have not received the pharmaceutical composition and a concurrent lipid
17 altering therapy,” and cannot anticipate the independent claim of the '399 patent. In fact, the
18 example of the methods of WO '118 expressly teaches a statin/EPA co-therapy. Because the
19 dependent claims depend from the independent claim, they include the elements of the

21 ¹⁹¹³ HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of
22 drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

23 ¹⁹¹⁴ WO '118 at 9 (emphasis added).

24 ¹⁹¹⁵ *Id.* at 10.

¹⁹¹⁶ *Id.* at 24-25.

1 independent claim. Thus, WO '118 cannot anticipate any of the dependent claims of the '399
2 patent.

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

5 WO '118 further does not anticipate the claims of the '399 patent because it does not
6 disclose "administering orally to the subject." As WO '118 fails to disclose the subject as
7 claimed, it cannot anticipate oral administration to the claimed "subject."

8 WO '118 additionally cannot anticipate the claims of the '399 patent because it does not
9 disclose administering the pharmaceutical composition at a dose of about 4g per day.

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

22 As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of
23 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The
24 court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic

1 range of 330 to 450 °C,”¹⁹¹⁷ and therefore failed to anticipate the claimed range. The court in
2 *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate
3 the patent’s claimed range of 0.1 to 5.0 percent.¹⁹¹⁸ The court explained that “although there is a
4 slight overlap, no reasonable fact finder could determine that this overlap describes the entire
5 claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are
6 different, not the same. . . . Thus, there is no anticipation.”¹⁹¹⁹ Similarly, although there may be
7 some overlap between the daily dose disclosed by WO ‘118 and the dose claimed by the ‘399
8 patent, WO ‘118 does not specifically highlight the overlapping area and, moreover, the range
9 claimed by the ‘399 patent does not fall within WO ‘118’s preferred range. Defendants
10 conveniently omit the preferred range and mischaracterize the teaching of WO ‘118. Notably,
11 the example indicates that up to 900 mg of the EPA composition could be used three times per
12 day (2.7 g). Thus, WO ‘118 does not expressly disclose the 4 g per day dose claimed by the ‘399
13 patent and cannot anticipate the independent claim of the ‘399 Patent.

14 WO ‘118 further does not anticipate the claims of the ‘399 patent because it does not
15 disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a
16 portion of the disclosure and exclude sections that show the breadth of WO ‘118’s teachings.
17 WO ‘118’s full disclosure recites that “the EPA-E used is preferably the one having a high
18 purity, for example, the one having the proportion of the EPA-E in the total fatty acid and
19 derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or
20 higher, and still more preferably 96.5% by weight or higher.”¹⁹²⁰ Therefore, WO ‘118 discloses

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22 ¹⁹¹⁷ *Atofina*, 441 F.3d at 1000.

23 ¹⁹¹⁸ *Id.*

24 ¹⁹¹⁹ *Id.*

¹⁹²⁰ WO ‘118 at 22.

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

4 The Federal Circuit has explained that “a preferred . . . range . . . that slightly overlaps the
5 . . . range claimed in the” patent is insufficient for anticipation.¹⁹²¹ In *Atofina*, the prior art
6 disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a
7 range between 330 and 450 degrees. The court explained that this slight overlap “is not
8 disclosed as . . . a species of the claimed generic range of 330 to 450 °C,”¹⁹²² and therefore failed
9 to anticipate the claimed range.¹⁹²³ The court in *Atofina* also found that a prior art disclosure of a
10 range of 0.001 to 1.0 percent failed to anticipate the patent’s claimed range of 0.1 to 5.0
11 percent.¹⁹²⁴ The court explained that “although there is a slight overlap, no reasonable fact finder
12 could determine that this overlap describes the entire claimed range with sufficient specificity to
13 anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no
14 anticipation.”¹⁹²⁵

15 Similarly, although there may be some overlap between the E-EPA content disclosed by
16 WO ‘118 and the ranges claimed by the ‘399 patent, WO ‘118 does not specifically highlight the
17 overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a
18 critical factor of the invention disclosed in the ‘399 patent. Therefore, WO ‘118’s broad
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21 ¹⁹²¹ *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

22 ¹⁹²² *Atofina*, 441 F.3d at 1000.

23 ¹⁹²³ *Atofina*, 441 F.3d at 1000.

24 ¹⁹²⁴ *Id.*

¹⁹²⁵ *Id.*

1 disclosure of the E-EPA content in its invention does not describe the claimed range with
2 sufficient specificity and cannot anticipate the independent claim of the '399 patent.

3 WO '118 is additionally insufficient for anticipation because it does not expressly
4 disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118
5 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is
6 DHA-E."¹⁹²⁶ The disclosure goes on to state that the composition of the invention is preferably
7 one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed
8 pharmaceutical composition is a critical factor of the invention disclosed in the '399 patent.

9 The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed
10 concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.
11 There is no express teaching or guidance directing the person of ordinary skill in the art to the
12 claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no
13 difference between the use of EPA or DHA in its invention, cannot anticipate the independent
14 claim of the '399 patent.

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

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¹⁹²⁶ WO '118 at 22.

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

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

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

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

1 inherently anticipate as a matter of law.”¹⁹²⁷ “[A]nticipation by inherent disclosure is appropriate
2 only when the reference discloses prior art that must *necessarily* include the unstated
3 limitation.”¹⁹²⁸ “It is not sufficient if a material element or limitation is ‘merely probably or
4 possibly present’ in the prior art.”¹⁹²⁹ Defendants fail to show that WO ‘118 “*necessarily*” meets
5 the recited claim elements relating to the administration step, the dosage form or characteristics
6 of the treated subject and the specific effect produced by the claimed method *every time*. WO
7 ‘118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total
8 cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in
9 the publication. Further, WO ‘118 is a translated Japanese disclosure that makes no reference to,
10 let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and
11 convincing evidence that the composition disclosed by WO ‘118 meets any dependent claim
12 elements.

13 3. The Claims of the ‘399 Patent Would Not Have Been Obvious In 14 Light of the Asserted References

15 Defendants identify 77 separate references that it asserts somehow render the claims of
16 the ‘399 Patent obvious.¹⁹³⁰ Defendants fail to demonstrate by clear and convincing evidence
17 that any of these references, alone or in combination, would render obvious any claims of the
18 ‘399 Patent. Defendants’ arguments rely on hindsight by impermissibly using the blueprint of
19
20

21 ¹⁹²⁷ *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

22 ¹⁹²⁸ *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

23 ¹⁹²⁹ *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

24 ¹⁹³⁰ Defendants’ Joint Invalidity Contentions at 13-25.

1 the '399 Patent itself to guide its combination of references.¹⁹³¹ Defendants chart a laundry list
2 of 77 separate references, without explanation. Defendants' disclosures do not comply with
3 Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly
4 establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs
5 cannot respond to undisclosed combinations and arguments.¹⁹³²

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

- 9 • 1) “. . .the asserted claims of the '399 patent would have been obvious over the
10 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
11 administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in
12 view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori
13 2000.”
- 14 • 2) “. . .the asserted claims of the '399 patent would have been obvious over the
15 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
16 administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku,
17 further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori
18 2000 and/or Maki.”
- 19 • 3) “. . .the asserted claims of the '399 patent would have been obvious over the
20 Omacor PDR/Lovaza PDR in combination with the known clinical benefits of
21 administering pure EPA as evidenced by Katayama in view of Satoh and/or in view
22 of Satoh or Shinozaki in further view of Contacos.”
- 23 • 4) “. . . the asserted claims of the '399 patent would have been obvious over WO '118
24 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the
Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000.”

20 ¹⁹³¹ *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) (“It is impermissible to use the claimed invention
21 as an instruction manual or ‘template’ to piece together the teachings of the prior art so that the claimed invention is
obvious.” (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

22 ¹⁹³² This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument,
23 including Defendants' attempt to incorporate by reference “the reasons set forth in the opposition proceedings for
24 EP 2 395 991 B1” in the European Patent Office. Such wholesale incorporation by reference does not satisfy the
Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that
each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to
rely on undisclosed or insufficiently disclosed references or argument.

- 1
- 2 • 5) “. . . the asserted claims of the ’399 patent would have been obvious over WO
 - 3 ’118, WO ’900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment
 - 4 regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and
 - 5 further in view of Katayama, Matsuzawa and/or Takaku.”

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

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

8 the time the invention was made to a person having ordinary skill in the art.”¹⁹³³ Obviousness is

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

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

11 claims at issue.¹⁹³⁴

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

13 teaches, including the portions that would lead away from the claimed invention.¹⁹³⁵ Indeed, any

14 teaching in the art that points away from the claimed invention must be considered.¹⁹³⁶ A

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

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

17 divergent from the path that was taken by the applicant.¹⁹³⁷ For instance, a reference teaches

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

19 unlikely to be productive of the result sought by the applicant.¹⁹³⁸

20 ¹⁹³³ 35 U.S.C. § 103(a).

21 ¹⁹³⁴ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

22 ¹⁹³⁵ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹⁹³⁶ *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

24 ¹⁹³⁷ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

¹⁹³⁸ *Id.*

1 In order to find obviousness based on a combination of references, there must be some
2 rationale for combining the references in the way claimed that is separate and apart from the
3 hindsight provided by the patented invention itself.¹⁹³⁹ The law prohibits an obviousness
4 challenge based on a hindsight reconstruction of the claimed invention from isolated prior art
5 references. It is improper for “the claims [to be] used as a frame, and individual, naked parts of
6 separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed
7 invention.”¹⁹⁴⁰ “The invention must be viewed not after the blueprint has been drawn by the
8 inventor, but as it would have been perceived in the state of the art that existed at the time the
9 invention was made.”¹⁹⁴¹

10 “The determination of obviousness is made with respect to the subject matter as a whole,
11 not separate pieces of the claim.”¹⁹⁴² “[A] patent composed of several elements is not proved
12 obvious merely by demonstrating that each of its elements was, independently, known in the
13 prior art.”¹⁹⁴³ “This is so because inventions in most, if not all, instances rely upon building
14 blocks long since uncovered, and claimed discoveries almost of necessity will be combinations
15 of what, in some sense, is already known.”¹⁹⁴⁴

16 Accordingly, it is improper to pick and choose isolated elements from the prior art and
17 combine them so as to yield the invention¹⁹⁴⁵ or to modify a prior art reference in a way that

19 ¹⁹³⁹ *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

20 ¹⁹⁴⁰ *See W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)

21 ¹⁹⁴¹ *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

22 ¹⁹⁴² *Sanofi Syntheolabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008)

23 ¹⁹⁴³ *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1369 (Fed. Cir. 2012) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007))

24 ¹⁹⁴⁴ *KSR*, 550 U.S. at 418-419.

¹⁹⁴⁵ *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

1 “would destroy the fundamental characteristics of that reference.”¹⁹⁴⁶ Moreover, a combination
2 is not obvious where “it would be impossible to apply these teachings [of the secondary
3 reference] to the [primary reference] without entirely changing the basic mechanism and
4 procedure thereof,”¹⁹⁴⁷ or where the proposed combination requires “material and radical
5 modification in order to conform to [the patentee’s] claims” or a “total reconstruction” of the
6 prior art device.¹⁹⁴⁸ Furthermore, it is improper “to modify the secondary reference before it is
7 employed to modify the primary reference” in assessing obviousness.¹⁹⁴⁹

8 Further, a party asserting obviousness in view of a combination of prior art disclosures
9 must show that a person of ordinary skill in the relevant field had an “apparent reason” to
10 combine the elements in the manner claimed¹⁹⁵⁰ and “a reasonable expectation of success.”¹⁹⁵¹

11 For chemical compounds, there must have been a reason both to select the prior art
12 compound “most promising to modify” and to make the necessary changes to arrive at the
13 claimed compound.¹⁹⁵² This protects against the use of hindsight to pick through the prior art
14

15 ¹⁹⁴⁶ *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

16 ¹⁹⁴⁷ *In re Irmischer*, 262 F.2d 85, 87 (CCPA 1958)

17 ¹⁹⁴⁸ *Id.* at 88.

18 ¹⁹⁴⁹ *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

19 ¹⁹⁵⁰ *KSR*, 550 U.S. at 417–19; *TriMed, Inc. v. Stryker Corp.*, 608 F.3d 1333, 1341 (Fed. Cir. 2010). Hindsight may
20 not be employed to identify relevant prior art and relevant teachings therein: *Heidelberger Druckmaschinen AG v.*
Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1071–72 (Fed. Cir. 1994); *Monarch Knitting Mach. Corp. v. Sulzer*
Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998).

21 ¹⁹⁵¹ *Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, “P&G”);
Takeda Chem. Indus. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a
22 combination of elements “must do more than yield a predictable result;” combining elements that work together “in
an unexpected and fruitful manner” would not have been obvious).

23 ¹⁹⁵² *Daiichi Sankyo Co. v. Matrix Labs. Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–
24 60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy’s Labs., Ltd.*, 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli*
Lilly & Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

1 based solely on structural similarity to the claimed compound.¹⁹⁵³ Any assertion of an “apparent
2 reason” must find a basis in the factual record.¹⁹⁵⁴

3 The “reasonable expectation of success” for a chemical compound must be of all of a
4 claimed compound’s relevant properties,¹⁹⁵⁵ including those discovered after the patent was filed
5 or even issued.¹⁹⁵⁶ “The basic principle behind this rule is straight-forward—that which would
6 have been surprising to a person of ordinary skill in a particular art would not have been
7 obvious.”¹⁹⁵⁷ Any assertion of a “reasonable expectation of success” must find a basis in the
8 factual record.¹⁹⁵⁸

9
10 ¹⁹⁵³ *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994
11 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co.*, 840 F.2d 902, 907 (Fed. Cir.
12 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int’l, Ltd. v. Solutia, Inc.*, 289 F.3d 1367, 1376 (Fed. Cir.
13 2002).

14 ¹⁹⁵⁴ *See, e.g., Vaidyanathan*, 381. at 993–94 (“[W]hile KSR relaxed some of the formalism of earlier decisions
15 requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did not remove the need to
16 anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the
17 references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi Sankyo*, 619 F.3d at
18 1354 (The assertion of a starting point “must avoid hindsight bias; it must look at the state of the art *at the time the*
19 *invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed
20 invention.” This turns on the known “properties and elements of the prior art compounds.”); *Forest Labs.*, 438
21 F.Supp.2d at 492–93 (rejecting defendants’ contention that claims to (+)-citalopram were “prima facie obvious in
22 light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding that
23 defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
24 motivated to resolve citalopram in June 1988”).

25 ¹⁹⁵⁵ *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) (“The success
26 of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . .
27 . [T]he ordinary medicinal chemist would not have expected famotidine to have the ‘most desirable combination of
28 pharmacological properties’ that it possesses.”); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d
29 820, 908 (S.D. Ind. 2005) (“[S]uccess was not simply finding a compound as active as clozapine . . . Here, the
30 ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of
31 pharmacological properties that it possesses.”).

32 ¹⁹⁵⁶ *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at
33 908.

34 ¹⁹⁵⁷ *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.”).

¹⁹⁵⁸ *See, e.g., Sanofi-Synthelabo*, 550 F.3d at 1089 (“Aptex argues that the district court applied an incorrect
inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were

1 In an obviousness determination, any objective indicia of nonobviousness must be taken
2 into account.¹⁹⁵⁹ An objective indicium is any “event[] proved to have actually happened in the
3 real world” that evidences the nonobvious nature of the invention.¹⁹⁶⁰ The existence of an
4 enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or
5 surprising results, expressions of skepticism, industry praise, commercial success, and copying
6 are classical indicia of nonobviousness.¹⁹⁶¹ These factual inquiries “guard against slipping into
7 use of hindsight,”¹⁹⁶² and “may often be the most probative and cogent evidence of
8 nonobviousness.”¹⁹⁶³

9 Also, as with assertions of anticipation, in order for an invention to be obvious, it must
10 have been fully “in possession” of the public—which requires that the claimed invention have
11 been enabled.¹⁹⁶⁴

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

17 ¹⁹⁵⁹ *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).

18 ¹⁹⁶⁰ *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

19 ¹⁹⁶¹ *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*
20 *Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005); *Panduit*, 810 F.2d at 1569; *In re Soni*, 54 F.3d 746, 750
(Fed. Cir. 1995); *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988); *Janissen*, 456 F.Supp.2d at 669–72.

20 ¹⁹⁶² *Graham*, 383 U.S. at 36.

21 ¹⁹⁶³ *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008) (quoting *Catalina Lighting*
22 *Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

22 ¹⁹⁶⁴ *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) (“[I]n order to render an invention unpatentable for
23 obviousness, the prior art must enable a person of ordinary skill to make and use the invention.”); *In re Hoeksema*,
24 399 F.2d 269, 274 (C.C.P.A. 1968) (“[I]f the prior art of record fails to disclose or render obvious a method for
making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound
itself is in the possession of the public.”).

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

4 a) General Overview

5 Defendants fail to provide a single prior art reference that discloses administration of the
6 recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population
7 (≥ 500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies,
8 many of which are not placebo controlled, which administer EPA, DHA, or both, in varying
9 degrees of purity, in a wide range of doses and administration periods, to subjects who have
10 baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance
11 of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo
12 controlled studies are considered the “gold standard” of clinical studies. Studies involving the
13 administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot
14 distinguish between the effect of the placebo from that of the active agent. Studies which
15 administer mixtures enriched for either EPA or DHA are not suitable for evaluating the
16 independent effects of EPA and DHA.¹⁹⁶⁵ Inconsistency in dosages and administration periods
17 and variations in the administered fatty acid compositions also complicate the interpretation of
18 the results and limit the application of these studies.

19 Defendants also rely on the ANCHOR study to argue that Amarin’s use of “patients with
20 very high TGs together with patients with high and borderline high TGs indicates that there is no
21 medical difference in responsiveness to treatment among the groups of people.”¹⁹⁶⁶ Defendants
22

23 ¹⁹⁶⁵ Mori 2006 at 96.

24 ¹⁹⁶⁶ Defendants’ Joint Invalidity Contentions at 533 (see FN 96).

1 mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-
2 controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in
3 patients with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) who were also on statin therapy.
4 Defendants point to the reported “Min-max” TG levels, 157-782 mg/dL, for the AMR101 4g
5 daily group to argue that Amarin used very-high TG patients with high and borderline-high TG
6 patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that
7 almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.¹⁹⁶⁷ In
8 addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were
9 reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use
10 the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a
11 person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the
12 very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to
13 ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels.
14 Contrary to Defendants’ assertion, the ANCHOR study does *not* indicate that there is no medical
15 difference in responsiveness to treatment between the very-high TG patient population and lower
16 TG patient populations merely because there was possibly one patient with baseline TG levels of
17 at least 500 mg/dL.

18 As discussed above in Section III, patients with very-high TG levels were considered
19 fundamentally different from patients with borderline-high or high TGs from a clinical,
20 regulatory, and therapeutic perspective.¹⁹⁶⁸ Clinically, the authoritative guidance to physicians

22 ¹⁹⁶⁷ FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6
23 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been
a few patients with TG > 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline
TG values < 500 mg/dL).

24 ¹⁹⁶⁸ See Bays Jan. 8, 2012 Decl., ¶ 20.

1 on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III
2 (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG;
3 high TG; and very high TG. The primary risk faced by borderline-high and high TG patients
4 was atherosclerosis, while the primary risk faced by very-high TG patients was acute
5 pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for
6 borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for
7 very-high TG patients was TG reduction. This distinction between patients with borderline-
8 high/high TG levels and patients with very high TG levels is also observed on the regulatory
9 level. The FDA recognized the different clinical status of the very-high TG population by
10 approving some drugs specifically for the very-high TG group without granting treatment
11 indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).¹⁹⁶⁹

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

18 Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but
19 *increase* LDL-C in very-high TG patients.¹⁹⁷⁰ The fibrate, Tricor (fenofibrate), for example,

22 ¹⁹⁶⁹ See Bays Jan. 8, 2012 Decl., ¶ 22.

23 ¹⁹⁷⁰ See Bays 2008 II, at 214-15 (noting that a fibrate caused LDL-C to go down in borderline-high group, remain
24 roughly the same in high TG group, and increase by around 50% in the very-high TG group).

1 decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)¹⁹⁷¹
 2 and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).¹⁹⁷² In
 3 patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-
 4 significant increase in LDL-C was observed.¹⁹⁷³ In patients with very-high TGs (mean baseline
 5 TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).¹⁹⁷⁴ Similar
 6 results were seen with the administration of Lopid (gemfibrozil).¹⁹⁷⁵ The differing effects of
 7 fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values
 8 demonstrates how a person of ordinary skill at the time of the invention would have understood
 9 that one could not simply assume that an observed effect of a TG-lowering agent on lipid
 10 parameters in patients with normal, borderline-high or high TG levels would be the same in
 11 patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or
 12 borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with
 13 normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-
 14 reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean
 15 baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level
 16 of 726 mg/dL) experience significantly increased LDL-C levels.

Fibrate	Mean Baseline TG Value	TG	LDL-C	HDL-C	Total-C
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19 ¹⁹⁷¹ Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

20 ¹⁹⁷² *Id.*

21 ¹⁹⁷³ *Id.* See also, Trilipix Label at 27.

22 ¹⁹⁷⁴ *Id.* See also, Trilipix Label at 27.

23 ¹⁹⁷⁵ 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).

Tricor (fenofibrate) ¹⁹⁷⁶	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.¹⁹⁷⁷ It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.¹⁹⁷⁸ 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%.¹⁹⁷⁹ Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.¹⁹⁸⁰

¹⁹⁷⁶ Tricor®, Physicians’ Desk Reference 502-505 (62d ed. 2008).

¹⁹⁷⁷ Chan 2002 I at 2379-81.

¹⁹⁷⁸ *Id.*; See also, Westphal at 918.

¹⁹⁷⁹ See Weintraub Sept. 7, 2011 Decl., ¶ 23 (citing Lovaza package insert); Bays May 16, 2011 Decl., ¶ 10; see also, Lovaza PDR and Omacor PDR.

¹⁹⁸⁰ See Pownall *et al.*, *Correlation of serum triglyceride and its reduction by ω-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins*, 143 *Atherosclerosis* 285, 295 (1999) (“Treatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by changing LDL structure; lowering serum [cholesterol ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C.”); Stalenhoef at 134 (stating that “Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable”); Harris 1997 at 389 (“The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however.” And “the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD”); Bays III at 248 (“No clinical trial data exist that this rise in LDL-C represents harm or potential “toxicity” to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty

1 Fibrates and prescription Omega-3 therapies demonstrate that one could not simply
2 assume that a lipid lowering agent would have the same effect in a patient with very-high TG
3 levels (≥ 500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They
4 also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when
5 the normal, borderline-high or high TG patient populations were administered omega-3 fatty
6 acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was
7 expected as a natural consequence of lowering TGs. A person of ordinary skill would have
8 considered the rise in LDL-C to be a direct consequence of TG lowering through increased
9 VLDL particle conversion.¹⁹⁸¹ Because normal to high TG patients did not have the large
10 backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not
11 expect LDL-C to increase in normal to high TG patients. It was also well known that the degree
12 of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor,
13 was linked to baseline TG levels; that LDL-C levels increased the most in patients with the
14 highest baseline TG levels¹⁹⁸² and did not increase for patients with lower TG levels. Therefore,
15 the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal,
16 borderline-high or high TG patients was *expected*.

17
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19 _____
20 acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C
21 levels (TC minus HDL-C.)”

21 ¹⁹⁸¹ Bays May 16, 2011 Decl., ¶ 11 (noting the “general knowledge in the art that omega-3 fatty acids as a class
22 increase LDL-C” in very-high TG patients); McKenney 2007, at 724 (“Because of the increase in LDL levels
23 observed in some patients treated with prescription omega-3, LDL levels also should be periodically assessed during
24 treatment.”); Bays in Kwiterovich at 247 (noting that increased LPL activity caused by fish oil “helps explain some
of the seemingly paradoxical lipid effects found with their clinical use, for example, the rise in LDL-C with the
decrease in VLDL.”).

¹⁹⁸² Bays 2008 I at 400-402.

1 Defendants contend that “a composition and its properties are inseparable, and therefore
2 do not impart any additional patentability,” and that “all of the limitations regarding the
3 properties of the ethyl EPA compound identified in the claims of the ‘399 patent are inherent to
4 the compound when administered to a human subject.”¹⁹⁸³ Inherency may not supply a missing
5 claim limitation in an obviousness analysis unless the inherency would have been obvious to one
6 of ordinary skill in the art.¹⁹⁸⁴ Obviousness is based on what is *known* in the art at the time of the
7 invention.¹⁹⁸⁵ It was not known or reasonably expected at the time of the claimed invention that
8 purified EPA, when administered to patients with very-high TG levels (≥ 500 mg/dL), would not
9 substantially increase LDL-C or would reduce Apo-B. Nor was EPA’s effect on LDL-C and
10 Apo-B necessarily present, or the natural result of the combination of elements explicitly
11 disclosed by the prior art.¹⁹⁸⁶ Therefore, inherency does not supply the missing claim elements
12 in the prior art cited by Defendants.

13 Defendants argue that the claims of the ‘399 patent which contain “a limiting clause, such
14 as ‘to effect’ or ‘is effective to,’” simply express the intended result of a process step positively
15 recited and therefore are not elements.¹⁹⁸⁷ This is incorrect. “There is nothing inherently wrong
16
17

18 ¹⁹⁸³ Defendants’ Joint Invalidation Contentions at 534.

19 ¹⁹⁸⁴ See, e.g., *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195–96 (Fed. Cir. 2014) (“A party must . . .
20 meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an
21 obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of
22 elements explicitly disclosed by the prior art.”); *In re Rijckaert*, 9 F.3d 1531, 1533–34 (Fed. Cir. 1993) (“The mere
23 fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency].”) (internal quotation omitted).

24 ¹⁹⁸⁵ *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.”).

¹⁹⁸⁶ See discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

¹⁹⁸⁷ Defendants’ Joint Invalidation Contentions at 535.

1 with defining some part of an invention in functional terms.”¹⁹⁸⁸ When a clause “states a
2 condition that is material to patentability, it cannot be ignored in order to change the substance of
3 the invention.”¹⁹⁸⁹ The claim term “to effect” acts as a positive limitation if the term represents
4 “unexpected and improved effects of administration of the claimed compound.”¹⁹⁹⁰ In addition,
5 the elements represent unexpected and improved effects of administration of purified EPA,
6 because a person of ordinary skill would not have expected no substantial increase in LDL-C or
7 reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the
8 requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded
9 patentable weight.

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

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

19 (1) WO ‘118

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

22 ¹⁹⁸⁸ See MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971)).

23 ¹⁹⁸⁹ *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005).

24 ¹⁹⁹⁰ *AstraZeneca AB v. Dr. Reddy’s Labs., Ltd.*, No. CIV.A.05-5553 JAP, 2010 WL 1981790, at *11–12 (D.N.J. May 18, 2010).

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
2 '118 disclose or suggest elements of the '399 Claims. The cited portions of WO '118 do not
3 disclose or suggest these elements at least because they do not disclose or suggest a first group of
4 subjects with the recited very high TG levels. The cited portions of WO '118 further do not
5 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 compositions or dosage. The cited portions of WO '118 further do not disclose or suggest a
7 method to effect the recited TG reduction without substantially increasing LDL-C based on a
8 comparison to a second group of subjects with the recited very high TG levels who have not
9 received the pharmaceutical composition and a concurrent lipid altering therapy.

10 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), WO '118
11 does not disclose or suggest a first group of subjects with the recited very high TG level. WO
12 '118 also does not disclose or suggest the claimed pharmaceutical composition with the recited
13 fatty acid composition or dosage. The cited portions of WO '118 further do not disclose or
14 suggest a method to effect the recited TG reduction without substantially increasing LDL-C
15 based on a comparison to a second group of subjects with the recited very high TG levels who
16 have not received the pharmaceutical composition and a concurrent lipid altering therapy.

17 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
18 second groups of subjects having the recited baseline LDL-C levels. With respect to Claims 6
19 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first
20 group of subjects with the claimed TG levels based on a comparison to the second group of
21 subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or
22 suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed
23 TG levels based on a comparison to the second group of subjects with the claimed TG level.
24

1 With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in
2 VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the
3 second group of subjects with the claimed TG level.

4 (2) WO '900

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

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO
7 '900 disclose or suggest elements of the '399 Claims. The cited portions of WO '900 do not
8 disclose or suggest these elements at least because they do not disclose or suggest a first group of
9 subjects with the recited very high TG levels. The cited portions of WO '900 further do not
10 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or
11 administration period. The cited portions of WO '900 further do not disclose or suggest a
12 method to effect the recited TG reduction without substantially increasing LDL-C based on a
13 comparison to a second group of subjects with the recited very high TG levels who have not
14 received the pharmaceutical composition and a concurrent lipid altering therapy.

15 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), WO '900
16 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does
17 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
18 dosage or administration period. WO '900 also does not disclose or suggest a method to effect
19 the recited TG reduction without substantially increasing LDL-C based on a comparison to a
20 second group of subjects with the recited very high TG levels who have not received the
21 pharmaceutical composition and a concurrent lipid altering therapy.

22 Further, with respect to Claim 2, this reference does not disclose or suggest
23 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
24 disclose or suggest the first and second groups of subjects having the recited baseline LDL-C

1 levels. With respect to Claim 5, this reference does not disclose or suggest the first and second
2 groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this
3 reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of
4 subjects with the claimed TG levels based on a comparison to the second group of subjects with
5 the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the
6 recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels
7 based on a comparison to the second group of subjects with the claimed TG level. With respect
8 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first
9 group of subjects with the claimed TG levels based on a comparison to the second group of
10 subjects with the claimed TG level.

11 (3) Contacos

12 Contacos describes a study designed to determine the safety and efficacy of a statin
13 (pravastatin) combined with fish oil either alone or in combination, for the management of
14 patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in
15 the claims.

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
17 Contacos disclose or suggest elements of the '399 Claims. The cited portions of Contacos do not
18 disclose or suggest these elements at least because they do not disclose or suggest a first group of
19 subjects with the recited very high TG levels. The cited portions of Contacos further do not
20 disclose or suggest the claimed pharmaceutical composition with the recited fatty acids
21 compositions, dosage, or administration period. The cited portions of Contacos further do not
22 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
23 the recited TG reduction without substantially increasing LDL-C based on a comparison to a
24

1 second group of subjects with the recited very high TG levels who have not received the
2 pharmaceutical composition and a concurrent lipid altering therapy.

3 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Contacos
4 does not disclose or suggest a subject with the recited very high TG level. Contacos also does
5 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 compositions, dosage, or administration period. Contacos also does not disclose or suggest a
7 method of administering the claimed pharmaceutical composition to effect the recited TG
8 reduction without substantially increasing LDL-C based on a comparison to a second group of
9 subjects with the recited very high TG levels who have not received the pharmaceutical
10 composition and a concurrent lipid altering therapy.

11 Further, with respect to Claim 2, this reference does not disclose or suggest
12 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
13 disclose or suggest the first and second groups of subjects having the recited baseline LDL-C
14 levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the
15 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
16 effect in the first group of subjects based on a comparison to the second group of subjects. With
17 respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed
18 pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group
19 of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this
20 reference fails to disclose or suggest the administration of the claimed pharmaceutical
21 composition to effect the recited reduction in VLDL-C in the first group of subjects based on a
22 comparison to the second group of subjects.

23
24
CONFIDENTIAL

1 (4) Grimsgaard

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

6 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
7 Grimsgaard disclose or suggest elements of the '399 Claims. The cited portions of Grimsgaard
8 do not disclose or suggest these elements at least because they do not disclose or suggest a first
9 group of subjects with the recited very high TG levels. The cited portions of Grimsgaard further
10 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
11 compositions or administration period. The cited portions of Grimsgaard further do not disclose
12 or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in
13 the first group of subjects with the recited very high TG level, based on a comparison to a second
14 group of subjects with the recited very high TG levels who have not received the pharmaceutical
15 composition and a concurrent lipid altering therapy.

16 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Grimsgaard
17 does not disclose or suggest a first group of subjects with the recited very high TG level.
18 Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the
19 recited fatty acid composition or administration period. The cited portions of Grimsgaard further
20 do not disclose or suggest a method to effect the recited TG reduction without substantially
21 increasing LDL-C in the first group of subjects with the recited very high TG level, based on a
22 comparison to a second group of subjects with the recited very high TG levels who have not
23 received the pharmaceutical composition and a concurrent lipid altering therapy.

24

1 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
2 second groups of subjects with the claimed TG levels having the recited baseline LDL-C levels.
3 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and
4 LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to
5 the second group of subjects with the claimed TG level. With respect to Claim 8, this reference
6 fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects
7 with the claimed TG levels based on a comparison to the second group of subjects with the
8 claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited
9 reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a
10 comparison to the second group of subjects with the claimed TG level.

11 (5) Hayashi

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

17 The portions of Hayashi cited by Defendants do not disclose or suggest elements of the
18 '399 patent claims. For example, the cited portions of Hayashi do not disclose or suggest
19 administration of EPA with the recited purity to a subject with the recited very high TG levels
20 who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject
21 had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or
22 suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
23 dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the
24 recited TG reduction without substantially increasing LDL-C in a subject with the recited very

1 high TG levels.

2 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Hayashi
3 does not disclose or suggest a first group of subjects with the recited very high TG level.
4 Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the
5 recited fatty acid compositions or dosage. Hayashi also does not disclose or suggest a method to
6 effect the recited TG reduction without substantially increasing LDL-C based on a comparison to
7 a second group of subjects with the recited very high TG levels who have not received the
8 pharmaceutical composition and a concurrent lipid altering therapy.

9 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
10 second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5,
11 this reference does not disclose or suggest the first and second groups of subjects having the
12 recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or
13 suggest the recited TG and LDL-C effect in the first group of subjects based on a comparison to
14 the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest
15 the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to
16 the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest
17 the recited reduction in VLDL-C in the first group of subjects based on a comparison to the
18 second group of subjects.

19 (6) Katayama

20 Katayama was directed to an investigation of the safety and efficacy of Epadel during
21 long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably,
22 Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and
23 was not placebo controlled.
24

1 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
2 Katayama disclose or suggest elements of the '399 Claims. The cited portions of Katayama do
3 not disclose or suggest these elements at least because they do not disclose or suggest a first
4 group of subjects with the recited very high TG levels. The cited portions of Katayama further
5 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
6 compositions or dosage. The cited portions of Katayama further do not disclose or suggest a
7 method to effect the recited TG reduction without substantially increasing LDL-C based on a
8 comparison to a second group of subjects with the recited very high TG levels who have not
9 received the pharmaceutical composition and a concurrent lipid altering therapy.

10 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Katayama
11 does not disclose or suggest a first group of subjects with the recited very high TG level.
12 Katayama also does not disclose or suggest the claimed pharmaceutical composition with the
13 recited fatty acid compositions or dosage. Katayama also does not disclose or suggest a method
14 to effect the recited TG reduction without substantially increasing LDL-C based on a comparison
15 to a second group of subjects with the recited very high TG levels who have not received the
16 pharmaceutical composition and a concurrent lipid altering therapy.

17 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
18 second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5,
19 this reference does not disclose or suggest the first and second groups of subjects having the
20 recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or
21 suggest the recited TG and LDL-C effect in the first group of subjects based on a comparison to
22 the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest
23 the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to
24

1 the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest
2 the recited reduction in VLDL-C in the first group of subjects based on a comparison to the
3 second group of subjects.

4 (7) Leigh-Firbank

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

8 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
9 Leigh-Firbank disclose or suggest elements of the '399 Claims. The cited portions of Leigh-
10 Firbank do not disclose or suggest these elements at least because they do not disclose or suggest
11 a first group of subjects with the recited very high TG levels. The cited portions of Leigh-
12 Firbank further do not disclose or suggest the claimed pharmaceutical composition with the
13 recited fatty acids compositions, dosage, or administration period. The cited portions of Leigh-
14 Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical
15 composition to effect the recited TG reduction without substantially increasing LDL-C based on
16 a comparison to a second group of subjects with the recited very high TG levels who have not
17 received the pharmaceutical composition and a concurrent lipid altering therapy.

18 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Leigh-
19 Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-
20 Firbank also does not disclose or suggest the claimed pharmaceutical composition with the
21 recited fatty acid compositions, dosage, or administration period. Leigh-Firbank also does not
22 disclose or suggest a method of administering the claimed pharmaceutical composition to effect
23 the recited TG reduction without substantially increasing LDL-C based on a comparison to a
24

1 second group of subjects with the recited very high TG levels who have not received the
2 pharmaceutical composition and a concurrent lipid altering therapy.

3 Further, with respect to Claim 2, this reference does not disclose or suggest
4 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
5 disclose or suggest the first and second groups of subjects having the recited baseline LDL-C
6 levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the
7 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
8 effect in the first group of subjects based on a comparison to the second group of subjects. With
9 respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed
10 pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group
11 of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this
12 reference fails to disclose or suggest the administration of the claimed pharmaceutical
13 composition to effect the recited reduction in VLDL-C in the first group of subjects based on a
14 comparison to the second group of subjects.

15 (8) Lovaza PDR

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

17 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
18 Lovaza PDR disclose or suggest elements of the '399 Claims. The cited portions of the Lovaza
19 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
20 the claimed pharmaceutical composition with the recited fatty acids compositions or
21 administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a
22 method of administering the claimed pharmaceutical composition to effect the recited TG
23 reduction without substantially increasing LDL-C based on a comparison to a second group of
24

1 subjects with the recited very high TG levels who have not received the pharmaceutical
2 composition and a concurrent lipid altering therapy.

3 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), the Lovaza
4 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
5 acid compositions or administration period. The Lovaza PDR also does not disclose or suggest a
6 method of administering the claimed pharmaceutical composition to effect the recited TG
7 reduction without substantially increasing LDL-C based on a comparison to a second group of
8 subjects with the recited very high TG levels who have not received the pharmaceutical
9 composition and a concurrent lipid altering therapy.

10 Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the
11 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
12 effect. With respect to Claim 8, this reference fails to disclose or suggest the administration of
13 the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B.
14 With respect to Claim 9, this reference fails to disclose or suggest the administration of the
15 claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

16 (9) Maki

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

19 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki
20 disclose or suggest elements of the '399 Claims. The cited portions of Maki do not disclose or
21 suggest these elements at least because they do not disclose or suggest a first group of subjects
22 with the recited very high TG levels. The cited portions of Maki further do not disclose or
23 suggest the claimed pharmaceutical composition with the recited fatty acids compositions,
24 dosage, or administration period. The cited portions of Maki further do not disclose or suggest a

1 method of administering the claimed pharmaceutical composition to effect the recited TG
2 reduction without substantially increasing LDL-C based on a comparison to a second group of
3 subjects with the recited very high TG levels who have not received the pharmaceutical
4 composition and a concurrent lipid altering therapy.

5 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Maki does
6 not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose
7 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions,
8 dosage, or administration period. Maki also does not disclose or suggest a method of
9 administering the claimed pharmaceutical composition to effect the recited TG reduction without
10 substantially increasing LDL-C based on a comparison to a second group of subjects with the
11 recited very high TG levels who have not received the pharmaceutical composition and a
12 concurrent lipid altering therapy.

13 Further, with respect to Claim 2, this reference does not disclose or suggest
14 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
15 disclose or suggest the first and second groups of subjects having the recited baseline LDL-C
16 levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the
17 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
18 effect in the first group of subjects based on a comparison to the second group of subjects. With
19 respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed
20 pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group
21 of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this
22 reference fails to disclose or suggest the administration of the claimed pharmaceutical
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1 composition to effect the recited reduction in VLDL-C in the first group of subjects based on a
2 comparison to the second group of subjects.

3
4 (10) Matsuzawa

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

7 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
8 Matsuzawa disclose or suggest elements of the '399 Claims. The cited portions of Matsuzawa
9 do not disclose or suggest these elements at least because they do not disclose or suggest a first
10 group of subjects with the recited very high TG levels. The cited portions of Matsuzawa further
11 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
12 compositions or dosage. The cited portions of Matsuzawa further do not disclose or suggest a
13 method of administering the claimed pharmaceutical composition to effect the recited TG
14 reduction without substantially increasing LDL-C based on a comparison to a second group of
15 subjects with the recited very high TG levels who have not received the pharmaceutical
16 composition and a concurrent lipid altering therapy.

17 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Matsuzawa
18 does not disclose or suggest a first group of subjects with the recited very high TG level.
19 Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the
20 recited fatty acid compositions or dosage. Matsuzawa also does not disclose or suggest a method
21 of administering the claimed pharmaceutical composition to effect the recited TG reduction
22 without substantially increasing LDL-C based on a comparison to a second group of subjects
23 with the recited very high TG levels who have not received the pharmaceutical composition and
24 a concurrent lipid altering therapy.

1 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
2 second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5,
3 this reference does not disclose or suggest the first and second groups of subjects having the
4 recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or
5 suggest the administration of the claimed pharmaceutical composition to effect the recited TG
6 and LDL-C effect in the first group of subjects based on a comparison to the second group of
7 subjects. With respect to Claim 8, this reference fails to disclose or suggest the administration of
8 the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in
9 the first group of subjects based on a comparison to the second group of subjects. With respect
10 to Claim 9, this reference fails to disclose or suggest the administration of the claimed
11 pharmaceutical composition to effect the recited reduction in VLDL-C in the first group of
12 subjects based on a comparison to the second group of subjects.

13 (11) Mori 2000

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

16 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
17 2000 disclose or suggest elements of the '399 Claims. The cited portions of Mori 2000 do not
18 disclose or suggest these elements at least because they do not disclose or suggest a first group of
19 subjects with the recited very high TG levels. The cited portions of Mori 2000 further do not
20 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
21 compositions or administration period. The cited portions of Mori 2000 further do not disclose
22 or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in
23 the first group of subjects with the recited very high TG level, based on a comparison to a second
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1 group of subjects with the recited very high TG levels who have not received the pharmaceutical
2 composition and a concurrent lipid altering therapy.

3 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Mori 2000
4 does not disclose or suggest a first group of subjects with the recited very high TG level. Mori
5 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited
6 fatty acid composition or administration period. The cited portions of Mori 2000 further do not
7 disclose or suggest a method to effect the recited TG reduction without substantially increasing
8 LDL-C in the first group of subjects with the recited very high TG level, based on a comparison
9 to a second group of subjects with the recited very high TG levels who have not received the
10 pharmaceutical composition and a concurrent lipid altering therapy.

11 Further, with respect to Claim 2, this reference does not disclose or suggest
12 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
13 disclose or suggest the first and second groups of subjects with the claimed TG levels having the
14 recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or
15 suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG
16 levels based on a comparison to the second group of subjects with the claimed TG level. With
17 respect to Claim 8, this reference fails to disclose or suggest the recited reduction in
18 Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison
19 to the second group of subjects with the claimed TG level. With respect to Claim 9, this
20 reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of
21 subjects with the claimed TG levels based on a comparison to the second group of subjects with
22 the claimed TG level.

23
24
CONFIDENTIAL

1 (12) Mori 2006

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

4 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori
5 2006 disclose or suggest elements of the '399 Claims. The cited portions of Mori 2006 do not
6 disclose or suggest these elements at least because they do not disclose or suggest a first group of
7 subjects with the recited very high TG levels. The cited portions of Mori 2006 further do not
8 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or
9 administration period. The cited portions of Mori 2006 further do not disclose or suggest a
10 method to effect the recited TG reduction without substantially increasing LDL-C based on a
11 comparison to a second group of subjects with the recited very high TG levels who have not
12 received the pharmaceutical composition and a concurrent lipid altering therapy.

13 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Mori 2006
14 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does
15 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
16 dosage or administration period. Mori 2006 also does not disclose or suggest a method to effect
17 the recited TG reduction without substantially increasing LDL-C based on a comparison to a
18 second group of subjects with the recited very high TG levels who have not received the
19 pharmaceutical composition and a concurrent lipid altering therapy.

20 Further, with respect to Claim 2, this reference does not disclose or suggest
21 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
22 disclose or suggest the first and second groups of subjects having the recited baseline LDL-C
23 levels. With respect to Claim 5, this reference does not disclose or suggest the first and second
24 groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this

1 reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of
2 subjects with the claimed TG levels based on a comparison to the second group of subjects with
3 the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the
4 recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels
5 based on a comparison to the second group of subjects with the claimed TG level. With respect
6 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first
7 group of subjects with the claimed TG levels based on a comparison to the second group of
8 subjects with the claimed TG level.

9 (13) Nozaki

10 Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The
11 purity of the composition is reported as 90%. The study was not placebo controlled and was
12 conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165
13 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG
14 patient population.

15 The portions of Nozaki cited by Defendants do not disclose or suggest elements of the
16 '399 patent claims. For example, the cited portions of Nozaki do not disclose or suggest
17 administration of EPA with the recited purity to a subject with the recited very high TG levels
18 who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do
19 not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
20 compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a
21 method to effect the recited TG reduction without substantially increasing LDL-C in a subject
22 with the recited very high TG levels.

23 Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the
24 '399 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least

1 because they do not disclose or suggest administration of EPA with the recited purity to a subject
2 with the recited very high TG levels who does not receive concurrent lipid altering therapy. The
3 cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical
4 composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki
5 further do not disclose or suggest a method to effect the recited TG reduction without
6 substantially increasing LDL-C.

7 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Nozaki
8 does not disclose or suggest a first group of subjects with the recited very high TG level. Nozaki
9 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
10 acid compositions or dosage. Nozaki also does not disclose or suggest a method to effect the
11 recited TG reduction without substantially increasing LDL-C based on a comparison to a second
12 group of subjects with the recited very high TG levels who have not received the pharmaceutical
13 composition and a concurrent lipid altering therapy.

14 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
15 second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5,
16 this reference does not disclose or suggest the first and second groups of subjects having the
17 recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or
18 suggest the recited TG and LDL-C effect in the first group of subjects based on a comparison to
19 the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest
20 the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to
21 the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest
22 the recited reduction in VLDL-C in the first group of subjects based on a comparison to the
23 second group of subjects.

24

1 (14) Omacor PDR

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

3 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the
4 Omacor PDR disclose or suggest elements of the '399 Claims. The cited portions of the Omacor
5 PDR do not disclose or suggest these elements at least because they do not disclose or suggest
6 the claimed pharmaceutical composition with the recited fatty acids compositions or
7 administration period. The cited portions of the Omacor PDR further do not disclose or suggest
8 a method of administering the claimed pharmaceutical composition to effect the recited TG
9 reduction without substantially increasing LDL-C based on a comparison to a second group of
10 subjects with the recited very high TG levels who have not received the pharmaceutical
11 composition and a concurrent lipid altering therapy.

12 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), the Omacor
13 PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
14 acid compositions or administration period. The Omacor PDR also does not disclose or suggest
15 a method of administering the claimed pharmaceutical composition to effect the recited TG
16 reduction without substantially increasing LDL-C based on a comparison to a second group of
17 subjects with the recited very high TG levels who have not received the pharmaceutical
18 composition and a concurrent lipid altering therapy.

19 Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the
20 administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C
21 effect. With respect to Claim 8, this reference fails to disclose or suggest the administration of
22 the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B.
23 With respect to Claim 9, this reference fails to disclose or suggest the administration of the
24 claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

1 (15) Satoh

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

5 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
6 Satoh disclose or suggest elements of the '399 Claims. The cited portions of Satoh do not
7 disclose or suggest these elements at least because they do not disclose or suggest a first group of
8 subjects with the recited very high TG levels. The cited portions of Satoh further do not disclose
9 or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or
10 dosage. The cited portions of Satoh further do not disclose or suggest a method to effect the
11 recited TG reduction without substantially increasing LDL-C in the first group of subjects with
12 the recited very high TG level, based on a comparison to a second group of subjects with the
13 recited very high TG levels who have not received the pharmaceutical composition and a
14 concurrent lipid altering therapy.

15 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Satoh does
16 not disclose or suggest a first group of subjects with the recited very high TG level. Satoh also
17 does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
18 composition or dosage. The cited portions of Satoh further do not disclose or suggest a method
19 to effect the recited TG reduction without substantially increasing LDL-C in the first group of
20 subjects with the recited very high TG level, based on a comparison to a second group of
21 subjects with the recited very high TG levels who have not received the pharmaceutical
22 composition and a concurrent lipid altering therapy.

23 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
24 second groups of subjects with the claimed TG levels having the recited baseline LDL-C levels.

1 With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and
2 LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to
3 the second group of subjects with the claimed TG level. With respect to Claim 8, this reference
4 fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects
5 with the claimed TG levels based on a comparison to the second group of subjects with the
6 claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited
7 reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a
8 comparison to the second group of subjects with the claimed TG level.

9 (16) Shinozaki

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

12 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
13 Shinozaki disclose or suggest elements of the '399 Claims. The cited portions of Shinozaki do
14 not disclose or suggest these elements at least because they do not disclose or suggest a first
15 group of subjects with the recited very high TG levels. The cited portions of Shinozaki further
16 do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
17 dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect the
18 recited TG reduction without substantially increasing LDL-C in the first group of subjects with
19 the recited very high TG level, based on a comparison to a second group of subjects with the
20 recited very high TG levels who have not received the pharmaceutical composition and a
21 concurrent lipid altering therapy.

22 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Shinozaki
23 does not disclose or suggest a first group of subjects with the recited very high TG level.
24 Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the

1 recited fatty acid dosage. The cited portions of Shinozaki further do not disclose or suggest a
2 method to effect the recited TG reduction without substantially increasing LDL-C in the first
3 group of subjects with the recited very high TG level, based on a comparison to a second group
4 of subjects with the recited very high TG levels who have not received the pharmaceutical
5 composition and a concurrent lipid altering therapy.

6 Further, with respect to Claim 2, this reference does not disclose or suggest
7 administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to
8 disclose or suggest the first and second groups of subjects having the recited baseline LDL-C
9 levels. With respect to Claim 5, this reference does not disclose or suggest the first and second
10 groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this
11 reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of
12 subjects with the claimed TG levels based on a comparison to the second group of subjects with
13 the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the
14 recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels
15 based on a comparison to the second group of subjects with the claimed TG level. With respect
16 to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first
17 group of subjects with the claimed TG levels based on a comparison to the second group of
18 subjects with the claimed TG level.

19 (17) Takaku

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

22 In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of
23 Takaku disclose or suggest elements of the '399 Claims. The cited portions of Takaku do not
24 disclose or suggest these elements at least because they do not disclose or suggest a first group of

1 subjects with the recited very high TG levels. The cited portions of Takaku further do not
2 disclose or suggest the claimed pharmaceutical composition with the recited fatty acid
3 compositions or dosage. The cited portions of Takaku further do not disclose or suggest a
4 method of administering the claimed pharmaceutical composition to effect the recited TG
5 reduction without substantially increasing LDL-C based on a comparison to a second group of
6 subjects with the recited very high TG levels who have not received the pharmaceutical
7 composition and a concurrent lipid altering therapy.

8 With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Takaku
9 does not disclose or suggest a first group of subjects with the recited very high TG level. Takaku
10 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty
11 acid compositions or dosage. Takaku also does not disclose or suggest a method of
12 administering the claimed pharmaceutical composition to effect the recited TG reduction without
13 substantially increasing LDL-C based on a comparison to a second group of subjects with the
14 recited very high TG levels who have not received the pharmaceutical composition and a
15 concurrent lipid altering therapy.

16 Further, with respect to Claim 4, this reference fails to disclose or suggest the first and
17 second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5,
18 this reference does not disclose or suggest the first and second groups of subjects having the
19 recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or
20 suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG
21 levels based on a comparison to the second group of subjects with the claimed TG level. With
22 respect to Claim 8, this reference fails to disclose or suggest the recited reduction in
23 Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison
24

1 to the second group of subjects with the claimed TG level. With respect to Claim 9, this
2 reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of
3 subjects with the claimed TG levels based on a comparison to the second group of subjects with
4 the claimed TG level.

5 c) The Prior Art Does Not Render the Claims Obvious

6 Defendants have not identified by clear and convincing evidence that the asserted claims
7 of the '399 Patent would have been *prima facie* obvious in light of the references cited, either
8 alone or in combination. As described above, none of the references discloses all of the elements
9 in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without
10 explanation, and argue they somehow must be combined to render obvious the asserted claims.
11 Where Defendants have failed to make disclosures with the specificity required by Local Patent
12 Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the
13 claim elements at issue.

14 Defendants' contentions fail to disclose each and every element of the claims of the '399
15 patent. Specifically, Defendants do not contend that the relied upon references disclose the
16 following elements of Claim 1 (and therefore Claims 2-9): *administering the claimed*
17 *pharmaceutical composition to the recited first group of subjects to effect a reduction in*
18 *triglycerides without substantially increasing LDL-C based upon a comparison to a second*
19 *group of subjects having a median fasting baseline triglyceride level of 500 mg/dl to about 1500*
20 *mg/dl who have not received the pharmaceutical composition and a concurrent lipid altering*
21 *therapy*. Therefore, Defendants' prior art combinations cannot render the claims *prima facie*
22 obvious.

23 Facts supporting the non-obviousness of the claims of the '399 patent are discussed in
24 detail below. The objective indicia discussed in Section V.O further demonstrate that the '399

1 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims
2 would have been obvious.

- 3 (1) Defendants Do Not Demonstrate that the Independent
4 Claim of the '399 Patent Would Have Been Obvious
 - 5 (a) Defendants Do Not Demonstrate that a Person of
6 Ordinary Skill in the Art Would Have Had Any
7 Reason to Replace the Mixed Fish Oil Active
8 Ingredient in Lovaza with Pure EPA
 - 9 (i) The '399 Patent is not Obvious Over the
10 Omacor PDR/Lovaza PDR, in Combination
11 with Katayama and/or Matsuzawa, Further
12 in View of Nozaki and/or Hayashi and
13 Further in View of Leigh-Firbank and/or
14 Mori 2000

15 With respect to the '399 Patent, Defendants present a combination of seven references:
16 "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering
17 pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or
18 Hayashi and further in view of Leigh-Firbank and/or Mori 2000."¹⁹⁹¹ Defendants also present
19 charts purporting to assert that an additional 61 references may be combined in order to render
20 the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary
21 skill would combine 61 separate references, they additionally do not identify any motivation for
22

23 ¹⁹⁹¹ Defendants' Joint Invalidation Contentions at 528.
24

1 combining these references.^{1992, 1993} Although Defendants need not point to an explicit statement
2 in the prior art motivating the combination of these references, any assertion of an “apparent
3 reason” to combine must find a basis in the factual record.¹⁹⁹⁴ Defendants’ unsupported cobbling
4 of selective disclosures represents hindsight reconstruction.¹⁹⁹⁵ Defendants’ contentions are no
5 more than an assertion that certain claim elements were known in the prior art. Throughout their
6 contentions, Defendants’ selectively cite to data points in a reference without considering other
7 disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

9
10 ¹⁹⁹² Defendants’ bare assertion that the asserted claims are obvious “in view of one or more of Omacor or Lovaza (as
11 described in the references cited above in section V.B.2 in view of, at least, the references cited in V.B.3 and 4,
12 including, the ‘954 publication, WO ‘900, WO ‘118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataka,
13 Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003,
14 Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006,
15 Rambjør, Sanders or Theobald,” similarly fails to meet the disclosure requirements of the Nevada Local Patent
16 Rules, and fails to provide any motivation to combine these references. *See* Defendants’ Joint Invalidity
17 Contentions at 528.

18 ¹⁹⁹³ Defendants’ bare assertion that “the motivation or reason to combine or modify the prior art to create
19 invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C,”
20 and that “[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person
21 having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references
22 or modifying references to render obvious the claimed inventions of the asserted claims,” fails to meet the disclosure
23 requirements of the Nevada Local Patent Rules. *See* Defendants’ Joint Invalidity Contentions at 526.

24 ¹⁹⁹⁴ *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).

¹⁹⁹⁵ *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under
KSR, “[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention
without any explanation as to how or why the references would be combined to produce the claimed invention”).

1 that it teaches.¹⁹⁹⁶ Accordingly, Defendants fail to meet their burden to establish *prima facie*
2 obviousness.

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

12 The proposed combinations do not render the independent claim of the '399 Patent
13 obvious and Defendants' burden to prove otherwise is especially difficult because the PTO
14 considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza
15 package insert specifically) during prosecution.¹⁹⁹⁷

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

18 (a) A Person of Ordinary Skill Would
19 Not Have Been Motivated to
20

21
22 ¹⁹⁹⁶ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

23 ¹⁹⁹⁷ *See, e.g., Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that “the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play”).

3 For an invention to be obvious, there must have been an “apparent reason” to make it.

4 The subject matter of the ‘399 patent claims would not have been obvious in light of these
5 references because a person of ordinary skill would not have been motivated to purify EPA or
6 been able to reasonably expect that the claimed pharmaceutical composition would reduce TG
7 levels without an increase in LDL-C levels.

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

12 Both Katayama and Matsuzawa are long term studies directed to an investigation of the
13 safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies
14 were not placebo controlled. A person of ordinary skill in the art understood that a placebo may
15 itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the
16 art would not and could not attribute any observed effect (and the magnitude of that effect) to
17 that of the drug. Any observed effect could be placebo dependent.¹⁹⁹⁸ As discussed above in
18 Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with
19 lower baseline TG levels—the subjects of Katayama and Matsuzawa—as in very-high TG
20 patients because patients with higher TG levels had different lipid responses compared to
21 patients with lower TG levels. Patients with very-high TG levels were considered fundamentally
22 different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical
23 guideline, regulatory, and therapeutic standpoint. As previously discussed, a person of ordinary
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¹⁹⁹⁸ 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.)

1 skill in the art would expect to see an increase in LDL-C levels when omega-3 fatty acids were
2 administered to patients with normal, borderline-high or high TG levels. Therefore, the prior art
3 Defendants rely upon to show that EPA did not increase LDL-C levels in normal, borderline-
4 high or high TG patients, was expected. At the priority date of the '399 patent, a person of
5 ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients
6 receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been
7 demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG
8 lowering through increased VLDL particle conversion.

9 Defendants argue that these studies disclose known “clinical benefits” of administering
10 pure EPA, lowering triglycerides without raising LDL-C.¹⁹⁹⁹ This is an incorrect characterization
11 of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of
12 long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels.
13 They do just that. They do not discuss any purported “benefits” observed related to LDL-C.
14 Defendants’ selective citation of LDL-C data from these references represents the improper use
15 of hindsight bias. A person of ordinary skill would understand the focus of Katayama and
16 Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw
17 conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C
18 levels at all. Defendants’ characterization of Katayama and Matsuzawa as disclosing the
19 lowering of TG levels without increasing LDL-C to be a “clinical benefit” is incorrect.²⁰⁰⁰ The
20 references don’t disclose or suggest that the LDL-C results obtained were a clinical benefit, nor
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23 ¹⁹⁹⁹ Defendants’ Joint Invalidation Contentions at 528-29.

24 ²⁰⁰⁰ Defendants’ Joint Invalidation Contentions at 528-29.

1 would a person of ordinary skill view these references as teaching such a benefit for very-high
2 TG patients.

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

7 In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The
8 purity of Epadel has varied over time and across different formulations of the product, therefore
9 it is difficult to determine the purity of the version of Epadel used unless it is specified by the
10 disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the
11 composition comprised at least about 96%, by weight of all fatty acids present, EPA, and
12 substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference
13 disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies.

14 Nishikawa,²⁰⁰¹ published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation.
15 Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite
16 purity.²⁰⁰²

17 Further, Katayama and Matsuzawa were small studies conducted in only Japanese
18 patients. These studies would not have been extrapolated to Western populations because the
19 Japanese diet contains much more fish and has a number of other different attributes. The
20 Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In
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22 ²⁰⁰¹ Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS*
23 *Analysis of PGI₂ and PGI₃ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

24 ²⁰⁰² See also, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

1 fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where
2 the patient population is exclusively Japanese cannot be generalized to other populations.²⁰⁰³
3 The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical
4 Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-
5 6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand
6 that the Japanese respond differently to lipid lowering agents than Westerners.

7 Defendants rely on Katayama to demonstrate the "known clinical benefits of
8 administering pure EPA - lowering triglycerides without raising LDL-C."²⁰⁰⁴ However,
9 Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term
10 treatment in patients with hyperlipidemia.²⁰⁰⁵ Katayama does not disclose *any* LDL-C related
11 data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that
12 reference to provide any such disclosure. The only results disclosed by Katayama were a
13 significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was
14 administered to patients with borderline-high to high TG levels, and its safety for long term use
15 in this patient population.²⁰⁰⁶ In addition to Katayama's lack of disclosure regarding LDL-C,
16 Defendants identify no other basis upon which a person of ordinary skill would have sought to
17 combine the composition disclosed in Katayama with the Lovaza PDR.

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21 ²⁰⁰³ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

22 ²⁰⁰⁴ Defendants' Joint Invalidity Contentions at 528.

23 ²⁰⁰⁵ Katayama at 2.

24 ²⁰⁰⁶ *Id.* at 16.

1 Defendants similarly rely on Matsuzawa to demonstrate the “known clinical benefits of
2 administering pure EPA - lowering triglycerides without raising LDL-C.”²⁰⁰⁷ However,
3 Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall
4 safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of
5 general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13
6 were evaluated for improvement in serum triglycerides levels.²⁰⁰⁸ It is unclear which of the 26
7 patients were included in each separate evaluation; therefore one cannot determine the baseline
8 lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack
9 of a placebo control makes it less likely that the results of this study can be generalized as an
10 effect on any population as a whole and provides no insight with respect to the very-high TG
11 patient population.

12 Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL,
13 and one participant with TG levels > 1,000 mg/dL.²⁰⁰⁹ However, when analyzing the lipid
14 impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL
15 because he was a “heavy drinker” and the “effect of alcohol made it impossible to assess
16 triglyceride levels.”²⁰¹⁰ Fig. 4, which depicts the changes in serum triglycerides, shows that the
17 mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500
18 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than
19 the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of
20 undisclosed purity). The identification of three patients with TG levels between 400 and less

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22 ²⁰⁰⁷ Defendants’ Joint Invalidation Contentions at 528.

23 ²⁰⁰⁸ Matsuzawa at 7 and 19.

24 ²⁰⁰⁹ *Id.* at 23.

²⁰¹⁰ *Id.* at 10.

1 than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of
2 ordinary skill would not understand that the reference makes any such disclosure. As discussed
3 above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG
4 less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no
5 evidence to the contrary.

6 Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a
7 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.²⁰¹¹ The disclosure
8 further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were
9 excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-
10 C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at
11 least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with
12 triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of
13 ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary
14 skill in the art, however, would have expected the same treatment in patients with very high TG
15 levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that
16 there have been conflicting results related to the LDL-C impact of EPA preparations that lowered
17 triglyceride levels.²⁰¹² At best, Matsuzawa demonstrates the uncertainty and confusion related to
18 the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify
19 any other basis upon which a person of ordinary skill would have sought to combine the
20 composition disclosed in Matsuzawa with the Lovaza PDR.

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²⁰¹¹ *Id.* at 11.

23 ²⁰¹² *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA
24 preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific
compositions used, or identify the patient populations were observed.

1 Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that
2 compositions comprising EPA as recited in the asserted claims lowers triglycerides without
3 substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA
4 increases LDL-C.²⁰¹³ Defendants identify no other basis upon which a person of ordinary skill
5 would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank
6 and/or Mori 2000 or reasonably expected that such a combination would successfully yield the
7 asserted claims of the '399 patent.

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

11 Defendants contend that the asserted claims of the '399 patent would have been obvious
12 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
13 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
14 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
15 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
16 very high TG patient population.

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

24 ²⁰¹³ See, e.g., Rambjor.

1 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
2 patient population were abnormally high and would not have relied upon these results. Further,
3 the person of skill in the art would not have looked to this patient population to predict the Apo-
4 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
5 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
6 levels.²⁰¹⁴ Nozaki does not provide a motivation or reasonable expectation of success for
7 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
8 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
9 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
10 to the very high TG patient population.

11 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
12 the EPA and the DHA content in the composition that was administered is unknown. A person
13 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
14 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
15 C were not statistically significant.²⁰¹⁵ Further, the person of skill in the art would not have
16 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
17 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
18 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
19 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
20 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
21 administered to the very high TG patient population.

23 ²⁰¹⁴ Nozaki at 256.

24 ²⁰¹⁵ Hayashi at 26, Table I.

1 Further, Hayashi was a small study conducted in only Japanese patients and was not
2 placebo controlled. This study would not have been extrapolated to Western populations
3 because the Japanese diet contains much more fish and has a number of other different attributes.
4 The Japanese consume a higher amount of EPA and DHA in their diets than Western
5 populations. In fact, Defendants' own reference states that the results from studies where the
6 patient population is exclusively Japanese cannot be generalized to other populations.²⁰¹⁶ The
7 Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical
8 Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6
9 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that
10 the Japanese respond differently to lipid lowering agents than Westerners.

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

16 (iii) Leigh-Firbank and/or Mori
17 2000 Do Not Disclose
18 Purported Knowledge that
19 DHA was Responsible for the
20 Increase in LDL-C

19 Defendants assert, incorrectly, that "it was known in the art as of February 2009 that
20 administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-
21 C levels."²⁰¹⁷ Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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23 ²⁰¹⁶ Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to
other populations.").

24 ²⁰¹⁷ Defendants' Joint Invalidity Contentions at 532.

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

14 Defendants rely upon Leigh-Firbank to demonstrate that it was known that “DHA was
15 responsible for the increase in LDL-C levels.” Leigh-Firbank, however, administered fish oil,
16 comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride
17 levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either
18 EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A
19 person of ordinary skill would similarly understand that Leigh-Firbank does not offer any
20 disclosure regarding the effect of EPA and DHA separately or gain any understanding of the
21 separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants)
22 acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated
23 and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA
24

1 and DHA.²⁰¹⁸ A person of ordinary skill would understand that studies directed to EPA and
2 DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on
3 lipid parameters. Defendants’ own prior art refutes the validity of the results disclosed by Leigh-
4 Firbank, because purified EPA and DHA were not administered separately.

5 Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent
6 effects of EPA and DHA individually, even though it administered a combination of EPA and
7 DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions
8 of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet
9 phospholipid EPA were *independently* associated with the decrease in fasting TGs,²⁰¹⁹ and DHA
10 is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state
11 of the art and numerous publications cited by Defendants.²⁰²⁰ It is widely accepted that DHA
12 also has a hypotriglyceridemic effect.

13 Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients
14 with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-
15 C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching
16 away from the claimed invention. “A reference may be said to teach away when a person of
17 ordinary skill, upon [examining] the reference, would be discouraged from following the path set
18 out in the reference, or would be led in a direction divergent from the path that was taken by the
19 applicant.”²⁰²¹ Although teaching away is fact-dependent, “in general, a reference will teach

21 ²⁰¹⁸ Mori 2006 at 96.

22 ²⁰¹⁹ Leigh-Firbank at 440.

23 ²⁰²⁰ See, e.g. Grimsgaard at 654.

24 ²⁰²¹ *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

1 away if it suggests that the line of development flowing from the reference’s disclosures is
2 unlikely to be productive of the result sought by the applicant.”²⁰²²

3 Mori 2000 concludes that the changes effected by DHA supplementation “may represent
4 a more favorable lipid profile than after EPA supplementation.”²⁰²³ For example, it states that
5 “DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL
6 cholesterol and a significant increase in the HDL₂-cholesterol subfraction, without adverse
7 effects on fasting glucose concentrations.”²⁰²⁴ Mori 2000 also states that “[d]espite an increase
8 in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may
9 be favorable.”²⁰²⁵ Therefore, based on the “favorable lipid profile” of DHA over EPA in Mori
10 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the
11 exact opposite of what Defendants argue in their contentions. Therefore, the art taught away
12 from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for
13 favoring or selecting DHA over EPA and highlight Defendants’ hindsight-driven focus on EPA,
14 despite disclosed advantages of DHA. A person of ordinary skill would take into consideration
15 the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias,
16 Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill
17 would consider. Defendants fail to identify any other basis upon which a person of ordinary skill
18 would have sought to combine Mori 2000 with the Lovaza PDR.

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21 ²⁰²² *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354
(Fed. Cir. 2012) (quoting *Gurley*); *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552 (Fed. Cir. 1983)
(“[P]roceed[ing] contrary to the accepted wisdom of the prior art ... is strong evidence of nonobviousness.”).

22 ²⁰²³ Mori 2000 at 1092.

23 ²⁰²⁴ Mori 2000 at 1088.

24 ²⁰²⁵ Mori 2000 at 1092.

1 factual record.²⁰²⁸ Defendants’ unsupported cobbling of selective disclosures represents
2 hindsight reconstruction.²⁰²⁹ Defendants’ contentions are no more than an assertion that certain
3 claim elements were known in the prior art. Throughout their contentions, Defendants’
4 selectively cite to data points in a reference without considering other disclosures or even the
5 reference as a whole. Each reference, however, must be evaluated for all that it teaches.²⁰³⁰
6 Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

7 The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method
8 of reducing triglycerides in a subject with the claimed pharmaceutical composition with the
9 recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR
10 further do not disclose a method to effect the claimed TG reduction without substantially
11 increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA
12 causes a significant increase in LDL-C levels in a very high TG patient population, for whom the
13 product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose
14 administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375
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16 ²⁰²⁸ See, e.g., *In re Vaidyanathan*, 381 F. App’x 985, 993–94 (Fed. Cir. 2010) (“[W]hile KSR relaxed some of the
17 formalism of earlier decisions requiring a ‘teaching, suggestion, or motivation’ to combine prior art references, it did
18 not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply
19 the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight.”); *Daiichi*
20 *Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point “must
21 avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to
22 select and then modify a lead compound to arrive at the claimed invention.” This turns on the known “properties and
23 elements of the prior art compounds.”) (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp.
24 2d 479, 492-93 (D. Del. 2006) (rejecting defendants’ contention that claims to (+)-citalopram were “*prima facie*
obvious in light of . . . claims [to] racemic citalopram” despite its use to “treat the same condition,” and concluding
that defendants “have not demonstrated by clear and convincing evidence that one skilled in the art would have been
motivated to resolve citalopram in June 1988.”), *aff’d*, 501 F.3d 1263 (Fed. Cir. 2007).

²⁰²⁹ 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”).

²⁰³⁰ *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

1 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500
2 mg/dL) TG levels. The proposed combinations do not render the independent claim of the '399
3 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the
4 PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both
5 generally and the Lovaza package insert specifically) during prosecution.²⁰³¹

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

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

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

16 (i) Grimsgaard, Katayama,
17 Matsuzawa and/or Takaku
18 Do Not Disclose Purported
19 Known Clinical Benefits of
20 Administering Pure EPA

19 Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the
20 "known clinical benefits of administering pure EPA - lowering triglycerides without raising
21 LDL-C." As discussed in Section V.D.3.c.1.a.i.a.i, incorporated herein by reference, Katayama

22 _____
23 ²⁰³¹ See, e.g., *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the
24 examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention.
Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear
and convincing standard came into play").

1 and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to
2 lower both serum total cholesterol and triglyceride levels. They do not discuss any purported
3 “benefits” observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that
4 the LDL-C results obtained were a clinical benefit.

5 Defendants also rely on Grimsgaard to support their assertion that “administration of
6 purified EPA-E reduced TG levels while minimally impacting the LDL-C levels.”²⁰³² However,
7 the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on
8 LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

9 Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA
10 administered to people with normal triglyceride levels for 7 weeks.²⁰³³ The results from the
11 Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the
12 net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that
13 DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid
14 supplements, which is consistent with previous studies which “suggested that serum HDL-C is
15 better maintained with oil rich in DHA than oil rich in EPA.”²⁰³⁴ Although Grimsgaard states
16 that EPA may produce a small decrease in serum total cholesterol, it does not specifically
17 comment on EPA’s effect on LDL-C.

18 Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to
19 characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in
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21 ²⁰³² Defendants’ Joint Invalidity Contentions at 532.

22 ²⁰³³ Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG
23 levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG
24 levels. (See Grimsgaard at Abstract (describing participants as “healthy”) and Table 4).

²⁰³⁴ 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.”²⁰³⁵ 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)		F test; P ^f	Contrasts between groups: P		
	Baseline	Change	Baseline	Change	Baseline	Change		DHA vs EPA	DHA vs corn oil	EPA vs corn oil
Triacylglycerols (mmol/L)	1.24 ± 0.58 ²	-0.22 ± 0.31 ²	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 ³	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

^f ANOVA for between-group comparisons of change.

² $\bar{x} \pm$ 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.”²⁰³⁶ 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

²⁰³⁵ Defendants’ Joint Invalidity Contentions at 532 n.93.

²⁰³⁶ Grimsgaard at 657.

1 patients with very-high triglycerides, because net decrease in triglycerides was consistently
2 greater for DHA and DHA caused a statistically significant increase in HDL-C when compared
3 to placebo. Grimsgaard states that “DHA may be responsible for the increase in HDL
4 cholesterol observed with some n-3 fatty acid supplements.”²⁰³⁷ Grimsgaard makes no such
5 statement regarding LDL-C.

6 Defendants cherry-pick results, regardless of whether the effect is found to be statistically
7 significant compared to placebo, in an attempt to force the studies to support their argument that
8 it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did
9 not. This illustrates the hindsight reasoning driving Defendants’ analysis of the prior art and
10 proposed combinations of prior art. Defendants point to a non-significant increase in DHA and
11 non-significant decrease in EPA in Grimsgaard as confirmation “that administration of purified
12 DHA results in increased LDL-C levels while administration of purified EPA resulted in a
13 decrease in LDL-C levels.” The results from Grimsgaard clearly show that EPA and DHA did
14 not have statistically significantly effects on LDL-C compared to placebo.²⁰³⁸ A person of
15 ordinary skill would not draw conclusions regarding differences between EPA and DHA based
16 on statistically insignificant results.

17 Defendants also rely on Takaku to support their assertion that “clinical benefits of
18 administering purified EPA—lowering triglycerides without raising LDL-C” was known in the
19

20 ²⁰³⁷ Grimsgaard at 654.

21 ²⁰³⁸In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a
22 statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to
23 interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have
24 argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make
such arguments for the obvious reason that it does not support their argument that EPA was known to have little or
no impact on LDL-C levels.

1 art.²⁰³⁹ Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and
2 safety of Epadel (of undisclosed purity)²⁰⁴⁰ based on long-term administration.²⁰⁴¹

3 A person of ordinary skill would not have concluded based on Takaku that EPA lowers
4 triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly
5 acknowledges that “only a few subjects were examined” and cautions against drawing a
6 conclusion “only from the results of the present study.”²⁰⁴² Because the study did not include
7 any placebo control, a person of ordinary skill in the art would understand these reports do not
8 provide the ability to conclude that the observed lipid effects would have occurred independent
9 of the drug that is administered. In addition, the study was conducted exclusively in Japanese
10 patients, and a person of ordinary skill would not have expected the results to be applicable to the
11 general population.²⁰⁴³

12 The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a
13 person of ordinary skill would not have expected the results to be applicable to patients with
14 triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because
15 measurement was not feasible due to “insufficient sample.”²⁰⁴⁴ It is possible that patients with
16 triglycerides above 500 mg/dL were among those excluded because of the challenges involved in
17

18 _____
19 ²⁰³⁹ Defendants’ Joint Invalidity Contentions at 529.

20 ²⁰⁴⁰ It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by
21 the claims. See Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%),
22 Nakamura at 23 (Epadel with purity > 90%).

23 ²⁰⁴¹ Takaku at ICOSAPENT_DFNDT00006834.

24 ²⁰⁴² Takaku at ICOSAPENT_DFNDT00006897.

²⁰⁴³ Yokoyama 2007 at 1097 (“[b]ecause our population was exclusively Japanese, we cannot generalise our results
to other populations.”)

²⁰⁴⁴ Takaku at ICOSAPENT_DFNDT00006884.

1 calculating LDL-C levels when triglyceride level is above 400 mg/dL.²⁰⁴⁵ Moreover, the study
2 does not provide different LDL-C graphs based on the baseline triglyceride levels.²⁰⁴⁶ Therefore,
3 it is impossible to determine whether the patients with triglycerides above 500 mg/dL had
4 increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C
5 change in patients with normal baseline LDL-C shows that the LDL-C change was volatile
6 throughout the study period, decreasing slightly at times but increasing by more than 8% at other
7 times.²⁰⁴⁷ Because of this volatility, a person of ordinary skill would not be able to conclude
8 what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in
9 LDL-C, stating only that the fluctuation in LDL-C was not significant.²⁰⁴⁸

10 A person of ordinary skill would not have concluded, based on Takaku, that purified EPA
11 had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has
12 “confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the
13 administration of *fish oil* to hypercholesterolemia patients.”²⁰⁴⁹ In contrast, Takaku states merely
14 that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary
15 skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study
16 was attributable to fish oil in general, not EPA specifically.

17 Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate
18 Defendants’ assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other
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20 _____
21 ²⁰⁴⁵ See Matsuzawa at ICOSPENT_DFNDTS00006450.

22 ²⁰⁴⁶ Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

23 ²⁰⁴⁷ Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

24 ²⁰⁴⁸ Takaku at ICOSAPENT_DFNDT00006897.

²⁰⁴⁹ Takaku at ICOSAPENT_DFNDT00006897.

1 studies cited by Defendants suggest that EPA increases LDL-C.²⁰⁵⁰ Defendants identify no other
2 basis upon which a person of ordinary skill would have sought to combine the Omacor
3 PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

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

7 Defendants contend that the asserted claims of the '399 patent would have been obvious
8 in view Nozaki and/or Hayashi in combination with other references, but they do not explain
9 why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted
10 claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a
11 reduction in triglycerides without increasing LDL-C when purified EPA is administered to the
12 very high TG patient population.

13 Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary
14 hypercholesterolemia subjects. A person of ordinary skill would not have found the results of
15 Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of
16 EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline
17 LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person
18 of skill in the art would not look to a study consisting of patients with baseline TG levels of 165
19 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.
20 Further, a person of ordinary skill would understand that the baseline LDL-C level in this small
21 patient population were abnormally high and would not have relied upon these results. Further,
22 the person of skill in the art would not have looked to this patient population to predict the Apo-

23 ²⁰⁵⁰ See, e.g., Rambjor.
24

1 B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of
2 1991, “[t]here is still controversy concerning the effects of fish oil” on LDL and HDL cholesterol
3 levels.²⁰⁵¹ Nozaki does not provide a motivation or reasonable expectation of success for
4 administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and
5 substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to
6 effect a reduction in triglycerides without increasing LDL-C when purified EPA is administered
7 to the very high TG patient population.

8 In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of
9 the EPA and the DHA content in the composition that was administered is unknown. A person
10 of ordinary skill would not have found the results of Hayashi reliable. The study involved 28
11 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-
12 C were not statistically significant.²⁰⁵² Further, the person of skill in the art would not have
13 looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very
14 high TG patients. Hayashi does not provide a motivation or reasonable expectation of success
15 for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA
16 and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,
17 to effect a reduction in triglycerides without increasing LDL-C when purified EPA is
18 administered to the very high TG patient population.

19 Further, Hayashi was a small study conducted in only Japanese patients and was not
20 placebo controlled. This study would not have been extrapolated to Western populations
21 because the Japanese diet contains much more fish and has a number of other different attributes.

23 ²⁰⁵¹ Nozaki at 256.

24 ²⁰⁵² Hayashi at 26, Table I.