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

AMARIN PHARMA, INC. *et al.*,

Plaintiffs,

v.

WEST-WARD PHARMACEUTICALS CORP., *et al*

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

## I. INTRODUCTION

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

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

[1] The asserted claims of the Patents-in-Suit were identified in Plaintiffs' Preliminary Infringement Contentions, served by Amarin on April 7, 2017.

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

Plaintiffs reserve the right to amend or supplement these contentions as discovery proceeds in this case, as the Court construes the claims, and as permitted by the Court and the Nevada Local Patent Rules. In particular, fact discovery has just begun, no depositions have taken place, nor has any expert discovery commenced. Further, claim construction proceedings have not yet begun and the Court has not construed the claims of the Asserted Patents.[2] Plaintiffs also reserve their right to amend or supplement these contentions in the event that Defendants amend their contentions to set forth additional combinations of references that it alleges render obvious any of the asserted claims, or in the event that any Defendant later produces references and/or amends its contentions to provide more specific information regarding any references. Furthermore, with respect to objective indicia of non-obviousness, Plaintiffs reserve the right to amend or supplement these contentions as discovery proceeds in this case. Plaintiffs further reserve their rights to amend or modify these contentions in the event that the Court adopts particular claim constructions.

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

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

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

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

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

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

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

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

[3] Defendants' Joint Invalidity Contentions at 24.

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

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

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

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[4] *See, e.g.,* Defendants' Joint Invalidity Contentions at 205-206.

[5] For example, Defendants' Joint Invalidity Contentions at pgs. 205 and 213 baldly state "It would have been 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 Invalidity Contentions at 9.

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

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

[7] Defendants' Joint Invalidity Contentions at 24.

[8] *Id*.

[9] *See* 37 C.F.R. § 1.56.

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

### A. Person of Ordinary Skill in the Art

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

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

### B. Priority Date of the Asserted Claims

The asserted claims are entitled to a priority date of no later than March 2008.[13] Any references cited by Defendants dated March 2008, or later, are therefore not prior art to the asserted claims.

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

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[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).

[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.").

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

[13] *See, e.g.*, AMRN01672057–58, AMRN01688238, AMRN01688512.

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

## III. STATE OF THE ART

### A. Introduction

The Patents-in-Suit relate to a drug named VASCEPA, which is designed to treat "severe (≥ 500 mg/dL) hypertriglyceridemia," a kind of lipid disorder in the blood. Lipids are fats found in the body, some of which circulate in the blood, including triglycerides ("TGs") and cholesterol. Because TGs and cholesterol are hydrophobic molecules, they move through the bloodstream in particles called "lipoproteins," which consist of a lipid core (TGs and cholesterol esters) coated with a layer of additional lipids (phospholipids and sphingomyelin), with various apolipoproteins attached, which determine lipoprotein function. There are five main types of 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% |

[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").

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

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

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

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[15] *Id.* at 393.

[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").

[17] *Id.*

[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").

[19] *Id.*

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

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

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

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[20] *Id.* at 3335.

[21] *Id.*

[22] *Id.*

[23] *Id.*

[24] *Id.*

[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.

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

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

B. **Key Concepts in Lipid Science**

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

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

[28] *See* 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 *in* Kwiterovich); 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").

[29] *See* Harold E. Bays, *Rationale for Prescription Omega-3-Acid Ethyl Ester Therapy for Hypertriglyceridemia: A 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.").

### 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

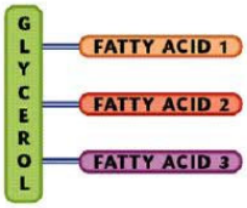
Fatty acids are the basic form of fat used by the body. While some fatty acids are synthesized in the body, others must be obtained from dietary sources. Fatty acids that are necessary to the body's health but cannot be produced by the body are referred to as "essential" fatty acids.

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 1[30]

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




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 |
|---|---|---|

[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.*

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

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

TG-depleted chylomicrons are smaller, denser and are referred to as "chylomicron remnants."[40] Chylomicron remnants return to the liver for further processing.[41]

[37] *Id.*

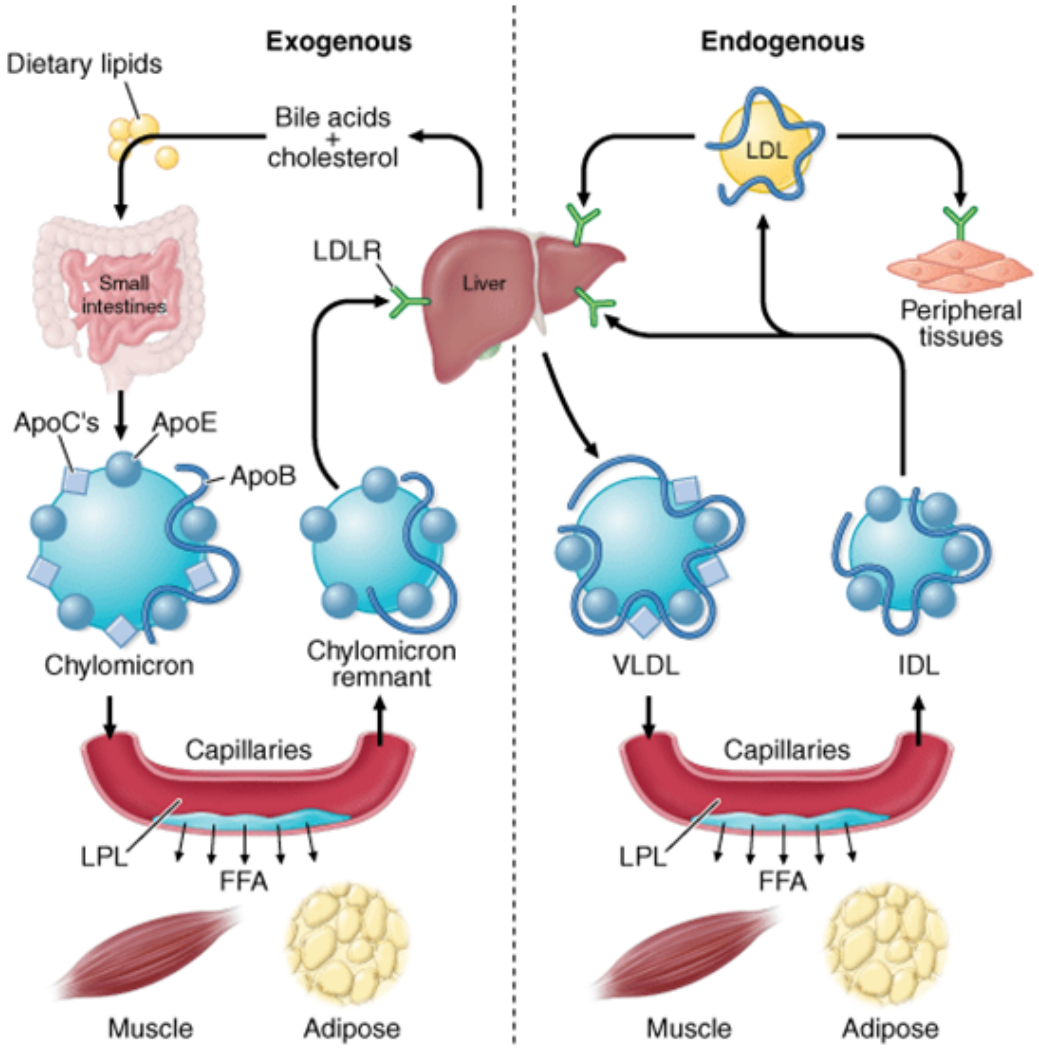
[38] *Id.*

[39] *Id.*

[40] *Id.*

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

**Figure 2**[42]




[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).

(2) VLDL, IDL, and LDL

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

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

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[43] Bays 2008 I, at 392.

[44] Kwiterovich *in* Kwiterovich, at 4; Rafael A. Cox & Mario R. Garcia-Palmieri, *Cholesterol, Triglycerides, and 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").

[45] Bays 2008 I, at 393.

[46] Kwiterovich *in* Kwiterovich, at 5.

[47] *Id.*

[48] Goodman & Gilman at 975.

[49] *Id.*

LDL particles generally account for about two thirds of a patient's total blood cholesterol.[50] Nearly half of all LDL particles are cleared from the bloodstream by the liver, while the rest (along with the cholesterol they carry: LDL-C[51]) are distributed throughout peripheral tissues and arteries, including coronary arteries.[52]

(3) HDL: The "good" cholesterol

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

**3. Dyslipidemia**

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

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[50] *Id.* at 976; ATP-III at 3163.

[51] When a "-C" is added to the lipoprotein abbreviations, reference is being made to the cholesterol carried by that lipoprotein.

[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").

[53] *Id.* at 13-4.

[54] *Id.*; ATP-III at 3163.

a) Hypertriglyceridemia

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

| **Classification**[55] | **Serum Triglyceride Levels** |
|---|---|
| Normal triglycerides | Less than 150 mg/dL |
| Borderline-high triglycerides | 150-199 mg/dL |
| High triglycerides | 200-499 mg/dL |
| Very-high triglycerides | ≥ 500 mg/dL |

b) Causation

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

(1) Genetic Disorders

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

[55] ATP-III at 3331.

[56] *Id.* at 3332 ("Many persons with very-high triglycerides have both overproduction and defective catabolism").

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

(2) Diet and Exercise

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

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

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

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

[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").

[60] McKenney 2005 at 13-6.

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

[62] ATP-III at 3179.

(3) Age and Gender

Age and gender were also known to have significant effects on baseline TG levels. Between birth and middle-age TG and cholesterol levels can increase 4-5 fold.[63] Further, in some countries, both TGs and cholesterol rise steadily between 20 and 50-60 years of age.[64]

Gender was also known to play a role in lipid levels. While men and women usually have similar levels of TGs and cholesterol from birth to 50 years of age, women tend to have higher values than men beyond age 50.[65] Women generally have higher HDL and lower VLDL particle levels than men.[66]

c) Risks of Hypertriglyceridemia: Atherosclerosis and Pancreatitis

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

(1) Atherosclerosis

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

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[63] *Classification of Hyperlipidaemias and Hyperlipoproteinaemias*, 43 BULLETIN OF THE WORLD HEALTH ORGANIZATION 891, 896 (1970) ("WHO").

[64] *Id.*

[65] *Id.*

[66] *Id.*; *see also* Kwiterovich *in* Kwiterovich at 8.

[67] *See* Rader *in* Topol, at 55; ATP-III at 3163.

[68] ATP-III at 3163.

Thus LDL-C was thought to make "the greatest contribution to the development of atherosclerotic risk."[69]

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

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

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[69] McKenney 2005 at 13-2.

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

[71] ATP-III at 3170.

[72] *Id.*

[73] *Id.* at 3169.

[74] *Id.* at 3170.

(2) Pancreatitis

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

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

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

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

[76] Cox at 154.

[77] *See* ATP-III at 3332.

[78] Bays *in* Kwiterovich, at 248.

[79] ATP-III at 3335.

[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).

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

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

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

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

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

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

[83] *Id*., ¶ 23.

[84] ATP-III at 3335.

[85] *Id.* at 3163.

[86] *Id.* at 3335.

[87] *Id.*

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

b) Very High TG Patients: Risk of Pancreatitis

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

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

[88] *Id.* at 3334-35.

[89] *Id.*

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

[91] *See* ATP-III at 3356; Weintraub May 23, 2011 Decl., ¶ 7 ("In patients with very-high [TGs], the initial aim of 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.

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

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

### 3. The FDA Followed the ATP-III Classifications in Reviewing TG Lowering Drugs

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

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[93] Weintraub Sept. 7, 2011 Decl., ¶ 8 ("[P]atients with borderline-high/high [TGs] . . . can respond very differently to [TG] lowering therapy than do subjects with very-high [TGs]."); Bays Jan. 8, 2012 Decl., ¶ 26 (referring to "the well-accepted scientific dogma that patients having the worst baseline metabolic abnormalities (whether it be high triglyceride levels, high glucose levels, etc.) often have the highest degree of responses to metabolic drug therapies, 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.

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

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

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

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

### D. Drugs Approved to Treat High TG Patients Prior to VASCEPA

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

#### 1. Niacin

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

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[96] *Id.*

[97] *See* ATP-III at 3333; *see also* Kwiterovich *in* Kwiterovich at 14.

[98] Kwiterovich *in* Kwiterovich at 14.

[99] Rader *in* Topol at 61.

[100] Goodman & Gilman at 991.

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

**2. Fibrates and Prescription Omega-3s**

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

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[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).

[102] Weintraub Sept. 7, 2011 Decl., ¶ 21.

[103] *Id.*

[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).

[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 [TG rich] particles are sometimes accompanied by an increase in LDL-C levels."); Goodman & Gilman at 993 (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 Hypertriglyceridemia*, 4 J. OF CARDIOVASCULAR RISK 385, 388 (1997) ("Harris 1997"); McKenny 2007 at 720.

a) Fibrates

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

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

[106] Weintraub Sept. 7, 2011 Decl., ¶ 14.

[107] Bays *in* Kwiterovich, at 247.

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

[109] *Id.*

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

[111] *See* Otvos *et al.*, *Low-Density Lipoprotein and High-Density Lipoprotein Particle Subclasses Predict Coronary Events and Are Favorably Changed by Gemfibrozil Therapy in the Veterans Affairs High-Density Lipoprotein 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).

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

| Fibrate | Mean Baseline TG Value | TG | LDL-C | HDL-C | Total-C |
|---|---|---|---|---|---|
| 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* |

* = $p < 0.05$ vs. Placebo

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

To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[116] This two-drug approach brought its own set of complications, however. Fibrates were known to be associated with a condition called

[112] Weintraub Sept. 7, 2011 Decl., ¶ 14 (noting that Lopid, Tricor, and Trilipix packaging all warned that LDL could increase significantly).

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

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

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

[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");

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

b) Prescription Omega-3s

(1) Composition

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

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[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.").

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

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

[120] *Id.* at ¶ 17

[121] *Id.*

[122] *Id.*

[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.

[124] Bays *in* Kwiterovich, at 246.

(2) Lovaza/Omacor

Prior to VASCEPA, FDA had approved only one prescription omega-3 fish oil indicated for very-high TG patients, which was made from a combination of approximately 465 mg EPA and 375 mg DHA.[125] Originally the drug was named "Omacor" (the name currently used in Europe), but because the name was too similar to another drug (Amicar), the named was changed to "Lovaza" in the United States in 2007.[126]

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

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[125] *See* Lovaza®, Physicians' Desk Reference 2699 (62d ed. 2007) ("Lovaza PDR"); Omacor®, Physicians' Desk Reference 2735 (60d ed. 2006) ("Omacor PDR").

[126] *See* July 2007 Letter from Reliant Pharmaceuticals to Pharmacy Professionals, http://www ncbop.org/PDF/OmacorBecomesLovazaJuly2007.pdf

[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").

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

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

[130] *See* Weintraub Sept. 7, 2011 Decl., ¶ 23.

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

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

Second, persons of ordinary skill in the art would also have been aware that, despite the increase in LDL-C, most clinical trial evidence demonstrated that omega-3 fatty acids decreased overall atherogenic cholesterol levels, as reflected by a reduction in non-HDL-C.[133] Because Lovaza lowered overall bad cholesterol (primarily through the reduction of VLDL particles and

[131] Bays *in* Kwiterovich, at 247; Harris *et al., Omega-3 fatty acids and Coronary Heart Disease Risk: Clinical and Mechanical Perspectives*, 197 ATHEROSCLEROSIS 12, 17-19 (2008) ("Harris 2008").

[132] 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.").

[133] Bays *in* Kwiterovich, at 248.

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

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

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

### E. A Person of Ordinary Skill Did Not Differentiate Between EPA and DHA's TG-Lowering Mechanism or LDL-C impact

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

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[134] *See id.*

[135] *Id.* at 254.

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

[137] *See* Bays 2008 I at 399.

[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.

[139] Bays 2008 I at 397.

collectively) reduced triglycerides by 30% to 40% and was a helpful adjunct to medications.[140] It was recommended that patients who needed to lower triglycerides take 2 to 4 g/day of *EPA and DHA* as capsules.[141]

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

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

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[140] Dunbar at 674; Bays I at 397.

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

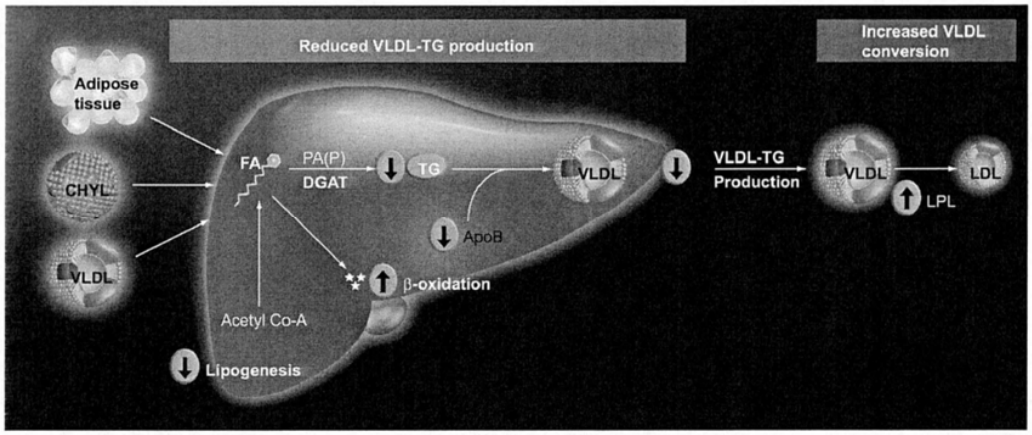
[142] Bays *in* Kwiterovich, at 248, Fig. 21.2.

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

[144] *See, e.g.* Dunbar; Bays 2008 I; Harris 2008; The Johns Hopkins Textbook of Dyslipidemia (Peter O. Kwiterovich Jr. Ed., 2009); Eslick et al., *Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis*, 136 INT'L J. CARDIOLOGY 4–16 (2009); Clemens von Schacky, *A review of omega-3 ethyl esters for 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")

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

Figure 3.[147]




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

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("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.").

[145] Harris 2008 at 16; Bays *in* Kwiterovich, at 247.

[146] Bays *in* Kwiterovich, at 247; Harris 2008 at 17-19.

[147] *See* Bays 2008 I at 396; Bays *in* Kwiterovich, at 248.

[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 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.)

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

A person of ordinary skill in the art also understood that omega-3 fatty acids, generically, improved the transformation of VLDL to LDL by increasing LPL activity, thereby aiding TG removal from VLDL (and chylomicron particles).[151] In fact, it was known that omega-3 fatty acids, when given individually (4g/day), both significantly increased the rate of chylomicron clearance.[152] Specifically, prescription omega-3 fatty acid therapy, such as Lovaza/Omacor, was thought to increase the conversion of VLDL to IDL and LDL.[153] A person of ordinary skill understood that the increased conversion of VLDL to LDL was the reason for the increased LDL-C levels in patients with very-high TGs levels when administered EPA and DHA.[154] It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty

[149] Bays 2008 I, 398 (A review of studies using rats showed that EPA and DHA in combination reduced lipogenesis 8 out of 8 times; EPA reduced lipogenesis 3 out of 4 times; and DHA reduced lipogenesis 2 out of 2 times.)

[150] Bays 2008 I, 399; Bays III at 247.

[151] Bays 2008 I at 399; Bays III at 247.

[152] Harris 2008 at 17-18.

[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.

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

### 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

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

Figure 3[159]

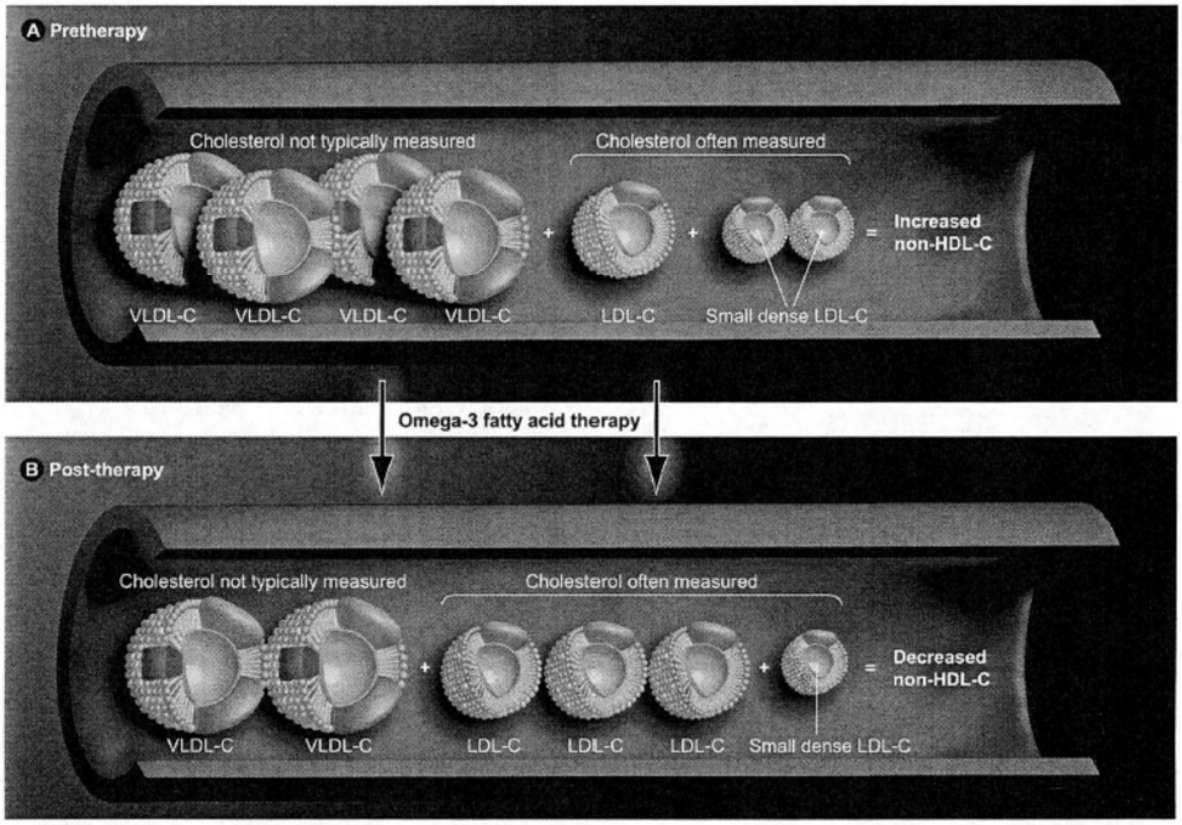
[155] Bays 2008 I at 400-402.

[156] Bays *in* Kwiterovich, at 248.

[157] Bays 2008 I at 402.

[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.*

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

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

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

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

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[162] *Id.*

[163] *See, e.g.,* Stalenhoef et al., *The Effect of Concentrated n-3 Fatty Acids Versus Gemfibrozil on Plasma Lipoproteins, Low Density Lipoprotein Heterogeneity and Oxidizability in Patients with Hypertrigliceridemia*, 153 ATHEROSCLEROSIS 129, 134 (2000); 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").

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

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

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

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

[166] *See, e.g.* Buckley *et al.*, *Circulating Triacylglycerol and ApoE Levels in Response to EPA and Docosahexaenoic Acid Supplementation in Adult Human Subjects*, 92 BR. J. NUTR 477, 479-481 (2004); Conquer & Holub, *Supplementation with an Algae Source of Docosahexaenoic Acid Increases (n-3) Fatty Acid Status and Alters Selected Risk Factors for Heart Disease in Vegetarian Subjects*, 126 J. of Nutr. 3032-3039 (1996); Hamazaki *et al.*, *Docosahexaenoic Acid-Rich Fish Oil Does Not Affect Serum Lipid Concentrations of Normolipidemic Young Adults*, 126 J. NUTR. 2784-2789 (1996); Grimsgaard *et al.*, *Highly Purified Eicosapentaenoic Acid and Docosahexaenoic 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.

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

## IV. DESCRIPTION OF REFERENCES

### A. General Overview

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

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

#### 1. Defendants Fail to Provide Studies Directed to the Very-High TG Patient Population

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

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

[170] *See e.g.,* Dunbar; Bays 2008 I; Harris 2008.

[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.

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

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

A person of ordinary skill in the art did not 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. In studies involving the borderline-high TG population (150-199 mg/dL), Lovaza/Omacor significantly reduced TGs and raised HDL-C,[173] but had no significant effect on other lipid-related variables, including LDL-C and Apo-B.[174] As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[175] Because normal to high TG patients do not have the large backlog of VLDL particles that very high TG patients

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[173] Chan 2002 I at 2379-81.

[174] *Id. See also*, Westphal at 918.

[175] 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.").

have, a person of ordinary skill would not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[176] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

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

[176] Bays 2008 I at 400-402.

[177] *See, e.g.* Matsuzawa at ICOSAPENT_DFNDTS00006450.

[178] *See, e.g.*, '594 Patent Reasons for Allowance; '521 Patent Reasons for Allowance; '225 Patent Reasons for Allowance.

### 2. Studies That Were Not Placebo Controlled

Many of the studies Defendants rely upon were not placebo controlled.[179] Randomized double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Without placebo, one cannot be certain that the observed lipid effects would not have occurred independent of the drug that is administered. For example, in Satoh, the administration of EPA caused a statistically significant reduction in LDL-C when compared to baseline; however, there was no significant effect when compared to placebo.[180] Likewise, in Grimsgaard, the administration of EPA caused a significant reduction of Apo-B compared to baseline; however, it was found to be non-significant when compared to placebo.[181] These discrepancies highlight the importance of a placebo-controlled study and why results compared only to baseline may be misleading.

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[179] *See, e.g.* Matsuzawa; Leigh-Firbank; Nozaki; Takaku *et al.*, Study on the Efficacy and Safety of Ethyl Icosapentate (MND-21) in Treatment of Hyperlipidemia Based on a Long-Term Administration Test, 7 J. CLIN. THERAPEUTICS &MEDICINE 191(1991) (translation provided by Defendants ICOSAPENT_DFNDTS00006864); Saito et al., *Effects of EPA on Coronary Artery Disease in Hypercholesterolemic Patients with Multiple Risk Factors: Sub-Analysis of Primary Prevention Cases from the Japan EPA Lipid Intervention Study (JELIS)*, 200 ATHEROSCLEROSIS 135-40 (2008); Shinozaki *et al., The Long-Term Effect of Eicosapentaenoic Acid on Serum Levels of Lipoprotein (a) and Lipids in Patients with Vascular Disease,* 2 J. ATHEROSCL. THROMB. 107-09 (1996) (translation provided by Defendants ICOSAPENT_DFNDTS00011751); Hayashi, *et al*., *Decreases in Plasma Lipid Content and Thrombotic Activity by Ethyl Icosapentate Purified from Fish Oils*, 56 CURR. THERAP. RES. 24-31 (1995); 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); 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); Okumura *et al., Eicosapentaenoic Acid Improves Endothelial Function in Hypertriglyceridemic Subjects Despite Increased Lipid Oxidizability,* 324 AM. J. MED. SCI. 247-53 (2002); Wojenski *et al.*, Eicosapentaenoic Acid Ethyl Ester as an Antithrombotic Agent: Comparison to an Extract of Fish Oil, 1081 BIOCHIM. BIOPHYS. ACTA. 33-38 (1991).

[180] 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).

[181] Grimsgaard at 653.

### 3. Japanese Studies

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

### 4. Studies That Administered EPA and DHA in Varying Concentrations

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

A few of the studies administered DHA-enriched oils which comprised DHA and a 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.

[183] Yokoyama *et al.*, Effects of Eicosapentaenoic Acid on Major Coronary Events in Hypercholesterolaemic Patients (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.").

[184] *See, e.g.,* Geppert; Maki *et al., Lipid responses to a dietary docosahexaenoic acid supplement in men and women 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*

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

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

*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).

[185] *See* Mori 2006 at 96.

[186] Maki at 197.

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

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

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

Many of the studies cited by Defendants administered only EPA[189] or only DHA[190] and studied its lipid effects. These types of studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on EPA-only or DHA-only studies to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

## B. Summary of Prior Art References[191]

### 1. WO '118[192]

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

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

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[189] *See, e.g.*, Katayama, Matsuzawa, Takaku, Saito, Yokoyama (w/ statin), Satoh, Shinozaki, Ando, Hayashi, Mataki (w/ statin), Nakamura, Nozaki, Okumura.

[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).

[191] For WO '118, Katayama, Matsuzawa, Shinozaki, and Takaku, Plaintiffs relied on the English translations 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.

[192] PCT Pub. App. WO 2007/142118 ("WO '118") (published Dec. 13, 2007).

[193] Defendants' Joint Invalidity Contentions at 43.

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

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

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

**2. WO '900[200]**

WO '900 was published in 2006. The publication is directed at a process of producing purified EPA from a culture of micro-organisms. It was considered by the USPTO during

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[194] WO '118 at 9.

[195] *Id.* at 8.

[196] *See* Section III.

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

[198] *Id.* at 22-23.

[199] *Id.* at 23.

[200] PCT Pub. App. WO 2008/004900 ("WO '900") (published Jan. 10, 2008).

prosecution of the asserted patents. Defendants argue that the publication "teaches the administration of pure EPA containing no DHA and that the presence of impurities, including DHA can reduce the effectiveness of EPA."[201]

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

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

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

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

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[201] Defendants' Joint Invalidity Contentions at 213.

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

[203] *Id.* at 5.

[204] *Id.* at 39.

### 3. Agren[205]

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

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

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

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[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).

[206] *Id.* at 767-68; Table 2.

[207] *Id.* at 768.

[208] *Id.* at 769.

[209] *Id.* at 770.

[210] *Id.*

#### 4. Ando[211]

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

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

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

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

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[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").

[212] Defendants' Joint Invalidity Contentions at 185.

[213] *Id.*

[214] Ando at 2183.

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

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

**5. Calabresi216**

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

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

Calabresi provides no motivation to use purified EPA instead of DHA. First, Calabresi did not differentiate EPA and DHA. Calabresi states that "[t]here is general agreement that

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[215] *See* Section III.

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

[217] Defendants' Joint Invalidity Contentions at 174-75.

[218] *Id.* at 175.

[219] *Id.*

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

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

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

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

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[220] Calabresi at 393.

[221] *Id.*

[222] *Id.* at 394.

[223] *Id.* at 393.

[224] *Id.* at 392.

### 6. Chan 2002 II[225]

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

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

Chan 2002 II does not show administration of 4 grams of a mixture of EPA and DHA to patients with TG above 500 mg/dL. The starting baseline TG level for the fish oil group was only 177 mg/dL. Therefore, Chan 2002 II does not provide a motivation or a reasonable expectation of success for administering 4 grams of EPA to patients with TG above 500 mg/dL.

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[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").

[226] Chan 2002 II at 433, Table 3.

[227] Defendants' Joint Invalidity Contentions at 215.

[228] *Id.*

[229] *Id.* at 229.

[230] *Id.* at 208, 258.

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

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

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

**7. Chan 2003[232]**

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

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[231] Chan 2002 II at 431.

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

[233] Chan 2003 at 303, Table 2.

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

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

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

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

Chan 2003 does not show that it was known that EPA and DHA had different effects on lipid metabolism as compared to one another. Chan 2003 attributes a common mechanisms for

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[234] Defendants' Joint Invalidity Contentions at 208, 258.

[235] *Id.* at 215.

[236] *Id.*

[237] *Id.* at 230.

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

**8. Childs[240]**

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

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

HDL-C decreased more in the EPA-rich pollock group than in the EPA-rich tuna and 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.

[239] *Id.* at 306.

[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").

[241] *Id.* at Table 5.

[242] *Id.* at 637.

[243] *Id.* at Table 6.

groups compared to the EPA-rich pollock group, "suggesting a lesser risk for heart disease on the tuna- and salmon-oil diets than on the pollock-oil diet."[244]

**9. Conquer 1996[245]**

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

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[244] *Id.* at 637.

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

[246] *Id.* at 3032.

[247] *Id.* at 3038.

[248] *Id.*

### 10. Contacos[249]

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

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

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[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").

[250] *Id.* at 1756.

[251] *Id.*

[252] *Id.*

### 11. Geppert[253]

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

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

A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[255] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.[256] Further, the DHA-rich oil contained other saturated and polyunsaturated fatty acids. As such, Geppert does not disclose the independent effects of DHA, 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").

[254] Defendants' Joint Invalidity Contentions at 75.

[255] Geppert at 784.

[256] *See also* Section III.

[257] *See* Mori 2006 at 96.

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

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

**12. Grimsgaard[259]**

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

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

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[258] Geppert at 784.

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

[260] Defendants' Joint Invalidity Contentions at 206.

maintained with oil rich in DHA than oil rich in EPA."[261] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

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

**13. Hamazaki[263]**

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

[261] Grimsgaard at 654.

[262] Defendants' Joint Invalidity Contentions at 79 and 184.

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

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

### 14. Hayashi[265]

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

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

A person of ordinary skill would not have been convinced that Hayashi discloses administration of purified EPA to patients with triglyceride levels above 500 mg/dL. It is true that Table I says that triglyceride level was 300 +/- 233 mg/dL at week 0.[269] The standard error of +/- 233 mg/dL is unusually high, and there is no explanation in Hayashi for such a high standard error. In fact, the correlation graphs in Figure 2 show no subject with triglyceride level 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.

[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").

[266] Defendants' Joint Invalidity Contentions at 210.

[267] *Id.* at 81.

[268] *Id.*

[269] Hayashi at 26.

[270] *Id.* at 28.

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

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

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

[271] *Id.* at 26, Table I.

[272] *Id.* at 28.

[273] *Id.* at 30.

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

**15. Katayama[274]**

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

Katayama does not disclose the purity of the Epadel used in the study. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel® used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel® was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and

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[274] Katayama *et al.*, *Efficacy And Safety Of Ethyl Icosapentate (Epadel®) Given For A Long Term Against Hyperlipidemia*, 21 PROG. MED. 457 (2001) ("Katayama").

[275] Defendants' Joint Invalidity Contentions at 206.

[276] Katayama at 2.

[277] *Id.* at 16.

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

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

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

**16. Kelley[280]**

In Kelley, 34 men with an average triglyceride level of 226 mg/dL participated in a double-blind, randomized, placebo-controlled parallel study. The DHA group received 7.5 g/day of DHA oil containing 3 g of DHA, and the placebo group received olive oil. Fasting lipid profiles were measured at the beginning of the study and after 90 days. Kelley did not

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

[279] *Id.* at 3.

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

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

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

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

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

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[281] Defendants' Joint Invalidity Contentions at 208.

[282] Defendants' Joint Invalidity Contentions. at 207.

[283] Defendants' Joint Invalidity Contentions at 221.

[284] Kelley at 329.

[285] *See* Mori 2006 at 96.

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

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[286] *Id.* at 329.

[287] *Id.*

[288] *Id.*

[289] *Id.* at 330.

[290] *Id.* at 332.

### 17. Kris-Etherton[291]

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. Kurabayashi[293]

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 estriol[294] (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.

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[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.

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

**19. Leigh-Firbank[298]**

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

Although Leigh-Firbank repeatedly admits that studies examining EPA and DHA's impact on lipid metabolism have produced conflicting results, it attempts to make conclusions regarding the effect of EPA and DHA alone, based on associations between platelet DHA and

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[296] Kurabayashi at 524–525.

[297] Kurabayashi at 525.

[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).

[299] Defendants' Joint Invalidity Contentions at 206.

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

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

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

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[300] *See, e.g.,* Leigh-Firbank at 436, 442 and 443.

[301] *See* Mori 2006 at 96.

[302] Leigh-Firbank at 440.

[303] Grimsgaard at 654

**20. Lovaza PDR[304]**

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

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

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

[304] Lovaza®, Physicians' Desk Reference 2699 (62d ed. 2007) ("Lovaza PDR")

[305] Lovaza PDR at 2700.

[306] *Id*.

[307] Defendants' Joint Invalidity Contentions at 46.

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

**21. Lovegrove[308]**

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

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

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

[309] Lovegrove at 974.

[310] Lovegrove at 978, table 2.

### 22. Maki[311]

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

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

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

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

[312] Defendants' Joint Invalidity Contentions at 194.

[313] Defendants' Joint Invalidity Contentions at 206.

[314] Maki at 197.

[315] Maki at 197.

of the other more beneficial effects of the capsules administered to the patients. Further, the increase in LDL-C was attributable to "an increase in cholesterol carried by larger, less dense particles."[316] There was a "near significant mean reduction in cholesterol carried by small, dense $LDL_3$ + $LDL_4$ particles in the DHA supplemented group . . . result[ing] in a significant net reduction in the DHA supplemented group, relative to controls, in the percentage of LDL cholesterol carried by small, dense particles."[317]

**23. Mataki[318]**

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

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

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[316] Maki at 195.

[317] *Id.*

[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).

[319] Defendants' Joint Invalidity Contentions at 186.

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

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

**24. Matsuzawa[322]**

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

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

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[320] Mataki at 36.

[321] *Id.*

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

[323] Defendants' Joint Invalidity Contentions at 206.

[324] Matsuzawa at ICOSAPENT_DFNDTS00006446 and ICOSAPENT_DFNDTS00006458.

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

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

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[325] *Id.* at ICOSAPENT_DFNDTS00006450.

[326] *Id.* at ICOSAPENT_DFNDTS00006454.

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

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

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

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

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[328] *Id.* at ICOSAPENT_DFNDTS00006462.

[329] *Id.* at ICOSAPENT_DFNDTS00006449.

[330] *Id*. at ICOSAPENT_DFNDTS00006450 and ICOSAPENT_DFNDTS00006473-74.

[331] *Id.* at ICOSAPENT_DFNDTS00006450.

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

**25. Mori 2000[332]**

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

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

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

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[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").

[333] Defendants' Joint Invalidity Contentions at 206.

[334] *Id.*

[335] Mori 2000 at 1088.

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[336] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the $HDL_2$-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[337] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[338] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions.

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

**26. Mori 2006[339]**

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

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[336] Mori 2000 at 1092.

[337] Mori 2000 at 1088.

[338] Mori 2000 at 1092.

[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).

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

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

[340] Defendants' Joint Invalidity Contentions at 116.

[341] Mori 2006 at 95-96.

[342] Defendants' Joint Invalidity Contentions at 115.

[343] Mori 2006 at 98.

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

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

Ultimately, based on its review of publications comparing the effects of EPA and DHA on cardiovascular health, Mori 2006 concludes that, "[b]oth [EPA and DHA] are equally effective in reducing serum triglycerides, but DHA and not EPA increased HDL cholesterol and, in particular, the $HDL_2$ cholesterol sub-fraction."[347] Furthermore, Mori 2006 discloses DHA's other beneficial effects on cardiovascular health. For example, Mori 2006 states that "DHA may be more favourable in lowering blood pressure and improving vascular function, raising HDL cholesterol and attenuating platelet function."[348] Based on the antiatherogenic and other cardiovascular benefits of DHA disclosed by Mori 2006, a person of ordinary skill would not have been motivated to use purified EPA over DHA or Lovaza. Again, Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified

[344] *Id.*

[345] *Id.*

[346] *Id.*

[347] *Id.* at 101.

[348] *Id.* at 101-102.

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

**27. Nakamura[350]**

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

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

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

Nakamura shows that a person of ordinary skill did not differentiate EPA from fish oil when discussing its lipid effects. Nakamura says that "fish oil can lower plasma lipid levels."[354]

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[349] *Id. at 98.*

[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).

[351] Defendants' Joint Invalidity Contentions at 217.

[352] Defendants' Joint Invalidity Contentions at 118-19.

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

[354] Nakamura at 22.

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

**28. Nelson[357]**

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

[355] *Id.* at 24.

[356] *Id.*

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

[358] Nelson at 1139.

[359] *Id.*

**29. Nestel[360]**

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

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

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

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

[361] Nestel at 328.

[362] *Id.*

[363] *Id.*

[364] Defendants' Joint Invalidity Contentions at 215-16.

[365] Defendants' Joint Invalidity Contentions at 229.

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

**30. Nozaki[366]**

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

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

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

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

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

### 31. Okumura[368]

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

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

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

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[367] Nozaki at 256.

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

[369] Defendants' Joint Invalidity Contentions at 210.

[370] May 7, 2012 Declaration of Phillip Lavin.

### 32. Omacor PDR[371]

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

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

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

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[371] Omacor®, Physicians' Desk Reference 2735 (60d ed. 2006) ("Omacor PDR").

[372] Omacor PDR at 2735.

[373] *Id.*

[374] Defendants' Joint Invalidity Contentions at 46.

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

**33. Park[375]**

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

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

Defendants contend that Park disclosed administering 4 grams of purified EPA daily[376] and that EPA and DHA were thought to have different effects on lipid metabolism as compared to another.[377] Defendants also contend that "[a]t the completion of the four weeks of treatment, administration with pure EPA resulted in decreased Apo-B-100 concentrations."[378]

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

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

[376] Defendants' Joint Invalidity Contentions at 197.

[377] *Id.* at 208.

[378] *Id.* at 128.

Park states that there was "no significant effect of treatment on fasting plasma TG, and total, HDL, LDL, and VLDL-C concentration."[379]

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

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

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

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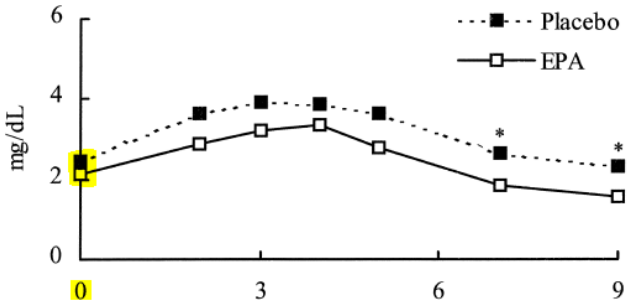
[379] Park at 457.

[380] Park at 461.

[381] *Id.*

[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. Rambjor[385]**

In Rambjor, 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. Rambjor 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).

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

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

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

**35. Saito[388]**

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

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

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[386] Defendants' Joint Invalidity Contentions at 208.

[387] Rambjor at 47.

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

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

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

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

[389] Defendants' Joint Invalidity Contentions at 218.

[390] Defendants' Joint Invalidity Contentions at 218.

[391] Defendants' Joint Invalidity Contentions at 219.

[392] Saito at 18.

[393] *Id.*

[394] *Id.* at 30.

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

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

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

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[395] *Id.* at 7.

[396] *Id.* at 16.

[397] *Id.*

[398] *Id.* at 18.

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

**36. Sanders[399]**

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

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

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

**37. Satoh[401]**

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

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

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

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[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).

[400] Defendants' Joint Invalidity Contentions at 137.

[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).

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

**38. Shinozaki[403]**

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

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

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

In Shinozaki, significant reduction in triglyceride levels did not occur until 18 months; significant reduction in total cholesterol levels did not occur until 6 months; and significant

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[402] *Id*. at 145.

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

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

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

**39. Takaku[405]**

Takaku was published in 1991. In the study, 2.7 g/day of Epadel (MND-21) was administered to 33 patients for the average period of 42 weeks, with the target administration period of 52 weeks and the minimum administration period of 24 weeks.[406] The purity of the Epadel used in the study was not specified. The subjects consisted of 16 males and 17 females with the average age of 56.[407] Of the 33 patients, 18 subjects were adopted for studying improvement in serum triglyceride, and 25 subjects were adopted for studying improvement in

[404] Shinozaki at 109.

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

[406] Takaku at ICOSAPENT_DFNDT00006875.

[407] *Id.*

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

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

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

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[408] Takaku at ICOSAPENT_DFNDT00006874.

[409] Defendants' Joint Invalidity Contentions at 206.

[410] Defendants' Joint Invalidity Contentions at 169.

[411] Takaku at ICOSAPENT_DFNDT00006897.

[412] Takaku at ICOSAPENT_DFNDT00006883, Fig. 14.

[413] Takaku at ICOSAPENT_DFNDT00006897.

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

A person of ordinary skill would not have concluded based on Takaku that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[418] In contrast, Takaku states merely

[414] Takaku at ICOSAPENT_DFNDT00006895.

[415] Takaku at ICOSAPENT_DFNDT00006875

[416] Takaku at ICOSAPENT_DFNDT00006884.

[417] Takaku ICOSAPENT_DFNDT00006882, Fig. 13.

[418] Takaku ICOSAPENT_DFNDT00006897.

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

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

**40. Theobald[420]**

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

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

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

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[419] *Id.*

[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).

[421] *Id*. at 560.

[422] *See* Mori 2006 at 96.

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

**41. Virani[425]**

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

Contrary to Defendants' contention that Virani discloses the correlation between Lp-PLA2 and Apo B levels,[428] Virani only states that "most of the Lp-PLA2 circulates bound to LDL via Apolipoprotein B."[429] Virani only discusses statin and fibrates, and does not mention omega-3 fatty acids or fish oil.[430] Virani shows that Lp-PLA2 was a novel biomarker and its

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[423] Theobald at 558 (emphasis added).

[424] *Id*. (emphasis added).

[425] Virani at 97.

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

[427] *Id.*

[428] Defendants' Joint Invalidity Contentions at 230.

[429] Virani at 98.

[430] Virani at 101-102.

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

**42. Wojenski[433]**

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

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

**43. Woodman[434]**

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

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[431] Virani at 102.

[432] Virani at 99.

[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).

[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).

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

### 44. Yokoyama 2007[436]

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

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

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

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[435] Woodman at 1011-1012.

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

[437] Defendants' Joint Invalidity Contentions at 218.

[438] Defendants' Joint Invalidity Contentions at 218.

[439] Yokoyama 2007 at 1095, Fig. 4.

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

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

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

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

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[440] *Id*. at 1095-1096.

[441] Yokoyama 2007 at 1096.

[442] *Id.*

### 45. Zalewski[443]

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

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

## V. Responses to Defendants' Joint Invalidity Contentions[449]

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

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

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[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).

[444] Defendants' Joint Invalidity Contentions at 230.

[445] Zalewski at 927.

[446] Zalewski at 928.

[447] Zalewski at 926.

[448] Zalewski at 928.

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

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

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

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

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[451] *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").

[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").

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

[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").

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

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 establish *prima facie* obviousness with the naked assertion that it would have been obvious to seek the particular claim element.

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

A. **The '728 Patent**

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

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

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

[456] *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.")

[457] *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.").

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

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

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

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[458] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all 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.").

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

[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.

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

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

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

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[464] *Id.*

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

[466] *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).

[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 (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 Invalidity Contentions at 199.

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

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

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

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

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

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

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

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

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

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

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

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

[476] *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).

[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).

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

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

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

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

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

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

[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).

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

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

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

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

[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).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

and vitality' to the claim."[490] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[491]

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

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

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[493] Thus, the entire preamble in the independent claims of the '728 must contain patentable weight.

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

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

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

[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 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").

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

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

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

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

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[494] WO '118 at 12.

[495] *Id.*

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

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

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '728 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and

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

the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[498] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[499] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as compared to the patent's claimed range of 0.1 to 5.0 percent.[500] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[501] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of

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

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

[500] *Id.*

[501] *Id.*

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

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

[502] *See* Section III.

[503] *Id.*

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

[505] *Id.*

[506] *Id.*

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

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

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

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[507] *Id.*

[508] Defendants' Invalidity Contentions at 46.

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

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

[510] WO '118 at 9 (emphasis added).

[511] *Id.* at 10.

[512] *Id.* at 24-25.

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

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

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

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

range of 330 to 450 °C,"[513] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[514] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[515] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '728 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '728 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '728 patent and cannot anticipate the independent claims of the '728 Patent.

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

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

[514] *Id.*

[515] *Id.*

[516] WO '118 at 22.

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

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

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '728 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '728 patent. Therefore, WO '118's broad

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

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

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

[520] *Id.*

[521] *Id.*

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

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

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

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

[522] WO '118 at 22.

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

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

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

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

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

### 3. The Claims of the '728 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '728 Patent obvious.[526] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '728 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of the

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

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

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

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

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

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

- 1) ". . .the asserted claims of the '728 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos)."

- 2) ". . .the asserted claims of the '728 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."

- 3) ". . .the asserted claims of the '728 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '728 patent would have been obvious over WO '118 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."

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

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

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

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[529] 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.[530]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[531] Indeed, any teaching in the art that points away from the claimed invention must be considered.[532] A reference teaches away if a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.[533] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[534]

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[529] 35 U.S.C. § 103(a).

[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).

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

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

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

[534] *Id*.

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

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[538] "[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."[539] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[540]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[541] or to modify a prior art reference in a way that

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

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

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

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

[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))

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

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

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

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[546] and "a reasonable expectation of success."[547]

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

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

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

[544] *Id*. at 88.

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

[546] *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).

[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 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).

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

based solely on structural similarity to the claimed compound.[549] Any assertion of an "apparent reason" must find a basis in the factual record.[550]

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

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[549] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381 Fed. App'x. 985, 994 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co*., 840 F.2d 902, 907 (Fed. Cir. 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int'l., Ltd. v. Solutia, Inc*., 289 F.3d 1367, 1376 (Fed. Cir. 2002).

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

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

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

[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

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

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[560]

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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.'").

[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).

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

[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 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.").

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

a) General Overview

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

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[562] Defendants

[561] Mori 2006 at 96.

[562] Defendants' Joint Invalidity Contentions at 211 (*see* FN 26).

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

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

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

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

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

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

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

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

[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).

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

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

| **Fibrate** | **Mean Baseline TG Value** | **TG** | **LDL-C** | **HDL-C** | **Total-C** |
|---|---|---|---|---|---|
| Tricor (fenofibrate)[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.)"

levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[577] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[578] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '728 patent are inherent to the compound when administered to a human subject."[579] Inherency may not supply a missing

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[577] 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.").

[578] Bays 2008 I at 400-402.

[579] Defendants' Joint Invalidity Contentions at 212.

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

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

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[580] *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).

[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.").

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

[583] Defendants' Joint Invalidity Contentions at 212.

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

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

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

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

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

(1) WO '118

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

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

[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).

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

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

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

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

(2) WO '900

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

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

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

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

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

(3) Contacos

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

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

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

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

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

(4) Grimsgaard

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

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

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

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

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

(5) Hayashi

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

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

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

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

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

(6) Katayama

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

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

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

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

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

(7) Leigh-Firbank

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

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

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

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

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

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

(8) Lovaza PDR

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

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

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

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

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

(9) Maki

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

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

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

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

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

(10) Matsuzawa

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

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

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

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

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

(11) Mori 2000

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

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

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

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

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

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

(12) Mori 2006

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

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

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

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

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

(13) Nozaki

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

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

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

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

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

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

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

(14) Omacor PDR

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

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

With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR further does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C. With respect to Claim 19, the Omacor PDR does not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited dosage of the recited pharmaceutical composition without concurrent lipid altering therapy, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition and concurrent lipid altering therapy.

Further, with respect to claims 7 and 14, this reference fails to disclose or suggest the recited reduction in fasting Lp-PLA2 in the subject based on a comparison to the second subject. With respect to Claims 15 and 17, this reference fails to disclose or suggest the subject and

second subject consume a Western diet. With respect to Claims 16 and 18, this reference fails to disclose or suggest the pharmaceutical composition with the recited fatty acid composition.

(15) Satoh

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

Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '728 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Satoh further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to a second subject with the claimed TG levels who has not received the claimed pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Satoh further does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. With respect to Claims 1 and 8, Satoh does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to a second subject with the claimed TG levels who has not received the claimed pharmaceutical composition and a concurrent lipid altering therapy. With respect to Claim 19,

Satoh does not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited dosage of the recited pharmaceutical composition without concurrent lipid altering therapy, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition and concurrent lipid altering therapy.

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

(16) Shinozaki

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

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

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

With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Shinozaki further does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. With respect to Claims 1 and 8, Shinozaki does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the subject with the claimed TG levels based on a comparison to a second subject with the claimed TG levels who has not received the claimed pharmaceutical composition and a concurrent lipid altering therapy. With respect to Claim 19, Shinozaki does not disclose or suggest a method that is effective to reduce the recited very high TG levels without substantially increasing LDL-C in a first patient population with the recited very high TG levels receiving the recited dosage of the recited pharmaceutical composition without concurrent lipid altering therapy, based on a comparison to a second patient population with the recited very high TG levels who has not received the pharmaceutical composition and concurrent lipid altering therapy.

Further, with respect to Claims 2 and 9, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 4 and 11, this reference fails to disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claims 5 and 12, this reference fails to disclose or suggest

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

(17) Takaku

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

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

With respect to Claims 1, 8 and 19 of the '728 Patent (and therefore all asserted claims), Takaku does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Takaku further does not disclose or suggest a method of

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

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

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '728 Patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '728 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 1 (and therefore Claims 2-7, 15 and 16): (1) a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl *who does not receive concurrent lipid altering therapy*; or (2) administering the claimed pharmaceutical composition to the recited subject to effect a reduction in triglycerides without substantially increasing LDL-C based on a comparison to a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who has not received the pharmaceutical composition and a concurrent lipid altering therapy.

In addition, Defendants do not contend that the relied upon references disclose the following elements of Claim 8 (and therefore Claims 9-14,17 and 18): (1) a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl *who does not receive concurrent lipid altering therapy*; or (2) administering a pharmaceutical composition to the recited subject to effect a reduction in fasting triglycerides of at least about 15% without substantially increasing LDL-C in the subject based upon a comparison to a second subject

having fasting triglyceride of 500 mg/dl to about 1500 who has not received the pharmaceutical composition and concurrent lipid altering therapy.

Further, Defendants do not contend that the relied upon references disclose the following elements of Claim 19: (1) a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl, *who does not receive a concurrent lipid altering therapy*; (2) administering a pharmaceutical composition that is effective to reduce in a first patient population receiving 4 g per day of said composition without concurrent lipid altering therapy and having said baseline triglyceride level, a median triglyceride level by at least 5% without substantially increasing LDL-C, compared to a median triglyceride level and LDL-C level observed in a second patient population having said baseline triglyceride level who has not received the pharmaceutical composition and concurrent lipid altering therapy.

Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '728 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '728 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claims of the '728 Patent Would Have Been Obvious

(a) Defendants Do Not Demonstrate that a Person of Ordinary Skill in the Art Would Have Had Any Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

(i) The '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

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[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, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald," similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 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."); *Daiichi*

reconstruction.[591] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[592] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

The proposed combinations do not render the independent claims of the '728 Patent 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 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).

[591] *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").

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

considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[593]

With respect to Claims 8 and 19, Defendants contend, without support, that "[a]s there is no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without increasing LDL-C, in this manner, with a reasonable expectation of success." Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[594] These contentions are inadequate to establish *prima facie* obviousness.

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[595] Defendants' burden to

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[593] *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").

[594] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris-Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

[595] *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

establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[596] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[597] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[598]

Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively. Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per

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to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

[596] 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).

[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.").

day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.[599] Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient population*, and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[600] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[601] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[602]

The analysis of the independent claims of the '728 Patent is incorporated into all asserted claims that depend from those Claims.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '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.

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[599] *See* Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

[600] *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").

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

[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

[603] *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.)

demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[604] This is an incorrect characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[605] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

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

[604] Defendants' Joint Invalidity Contentions at 206.

[605] Defendants' Joint Invalidity Contentions at 206.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[606] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[607]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[608] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty

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

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

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

acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[609] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[610] Katayama does not disclose *any* LDL-C related data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[611] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[612] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[613] It is unclear which of the 26

[609] Defendants' Joint Invalidity Contentions at 206.

[610] Katayama at 2.

[611] *Id.* at 16.

[612] Defendants' Joint Invalidity Contentions at 206.

[613] Matsuzawa at 7 and 19.

patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[614] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[615] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

[614] *Id.* at 23.

[615] *Id.* at 10.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[616] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[617] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[618] Defendants identify no other basis upon which a person of ordinary skill

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[616] *Id.* at 11.

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

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

would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '728 patent.

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

Defendants contend that the asserted claims of the '728 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol

levels.[619] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[620] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

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

[619] Nozaki at 256.

[620] Hayashi at 26, Table I.

patient population is exclusively Japanese cannot be generalized to other populations.[621] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

(iii) Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos) 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."[622] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As

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

[622] Defendants' Joint Invalidity Contentions at 209.

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

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contained other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[623] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid

[623] Mori 2006 at 96.

parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[624] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[625] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."[626] Although teaching away is fact-dependent, "in general, a reference will teach

[624] Leigh-Firbank at 440.

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

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

away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[627]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[628] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the $HDL_2$-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[629] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[630] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

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[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 (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.").

[628] Mori 2000 at 1092.

[629] Mori 2000 at 1088.

[630] Mori 2000 at 1092.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[631] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

Defendants purport to formulate an obviousness argument that relies on Satoh or Shinozaki in view of Contacos.[632,633] However, Defendants fail to provide any factual or legal basis as to why Satoh, Shinozaki, or Contacos disclose a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[634] or "a reasonable expectation of success"[635] of achieving the claimed invention.

Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and pravastatin, but it does not disclose administration of EPA of the recited composition. Contacos

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

[632] Defendants' Joint Invalidity Contentions at 206.

[633] Further, it is not apparent what combination or combinations of references Defendants assert in their purported obviousness argument based on "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)." In failing to identify the role of "Satoh or Shinozaki in view of Contacos" in this purported obviousness combination or offer any associated explanation, they have failed to meet their contentions burden. Accordingly, defendants should be precluded from relying on this purported combination.

[634] *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).

[635] *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).

demonstrated that fish oil does not increase LDL-C or Apo-B when administered to patients. Contacos also fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C or Apo-B.

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.[636] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. In addition, Satoh does not disclose the effect of EPA on Apo-B. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C or Apo-B.

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

[636] Satoh at 145.

states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[637] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Shinozaki says nothing about an LDL-C or Apo-B effect because it measured only LDL particle number and Lp(a), and did not measure LDL-C or Apo-B. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[638] In addition to Shinozaki's lack of disclosure regarding LDL-C or Apo-B, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Defendants identify no other basis upon which a person of ordinary skill would have sought to combine 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)."

(ii) The '728 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, in further view of Nozaki and/or

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

[638] Shinozaki at 107-109.

Hayashi and Further in View of Grimsgaard, Mori 2000 and/or Maki

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.*, *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").

elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[642] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '728 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[643]

With respect to Claims 8 and 19, Defendants contend, without support, that "[a]s there is no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without

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

[643] *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").

increasing LDL-C, in this manner, with a reasonable expectation of success." Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[644] These contentions are inadequate to establish *prima facie* obviousness.

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[645] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance"

[644] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

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

attached to the recited TG reduction amount.[646] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[647] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[648]

Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively. Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.[649] Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient population*, and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. Defendants discuss the claim

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[646] 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).

[647] *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).

[648] *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.").

[649] *See* Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

elements in isolation, and fail to address the claimed invention as a whole.[650] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[651] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[652]

The analysis of the independent claims of the '728 Patent is incorporated into all asserted claims that depend from those Claims.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '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) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported

[650] *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").

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

[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").

Known Clinical Benefits of Administering Pure EPA

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

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[653] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[654] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[655] Although Grimsgaard states that

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[653] Defendants' Joint Invalidity Contentions at 209.

[654] Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG levels. (*See* Grimsgaard at Abstract (describing participants as "healthy") and Table 4).

[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) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P$[1] | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[3] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[5] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[657] However, Grimsgaard does not conclude

[656] Defendants' Joint Invalidity Contentions at 209 n.22.

[657] Grimsgaard at 657.

that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that "DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements."[658] Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard as confirmation "that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[659] A person of

[658] Grimsgaard at 654.

[659] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make such arguments for the obvious reason that it does not support their argument that EPA was known to have little or no impact on LDL-C levels.

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

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[660] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[661] based on long-term administration.[662]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[663] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[664]

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

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[660] Defendants' Joint Invalidity Contentions at 206.

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

[662] Takaku at ICOSAPENT_DFNDT00006834.

[663] Takaku at ICOSAPENT_DFNDT00006897.

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

triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[665] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[666] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[667] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other times.[668] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[669]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[670] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary

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[665] Takaku at ICOSAPENT_DFNDT00006884.

[666] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[667] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

[668] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[669] Takaku at ICOSAPENT_DFNDT00006897.

[670] Takaku at ICOSAPENT_DFNDT00006897.

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

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[671] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

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

Defendants contend that the asserted claims of the '728 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

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

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

Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[672] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[673] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[672] Nozaki at 256.

[673] Hayashi at 26, Table I.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[674] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[675] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

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

[675] Defendants' Joint Invalidity Contentions at 209.

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

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[676] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[677] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with

[676] Defendants' Joint Invalidity Contentions at 206.

[677] Defendants' Joint Invalidity Contentions at 209.

below-average levels of HDL-C levels.[678] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated, monounsaturated and polyunsaturated fatty acids.[679] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[680] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have also contributed to the elevation in LDL cholesterol."[681] Further, Maki admits that the "mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[682] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

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

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[678] Maki at 190.

[679] Maki at 191.

[680] Maki at 195.

[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).

[682] Maki at 197.

less worrisome."[683] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[684]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[685] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(iii) The '728 Patent Is Not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or in View of Satoh or Shinozaki in Further View of Contacos

With respect to the '728 Patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[686] Defendants also present charts purporting to assert that an additional 60 references may be combined in order to render the Claims obvious. Not only do

[683] Maki at 197.

[684] Maki at 197.

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

[686] Defendants' Joint Invalidity Contentions at 206-07.

Defendants ignore the improbability that a person of ordinary skill would combine 60 separate references, they additionally do not suggest any identify for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent reason" to combine must find a basis in the factual record.[687] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[688] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[689] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

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[687] *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).

[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)

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

Defendants formulate an obviousness argument that relies on Contacos.[690] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[691] or "a reasonable expectation of success"[692] of achieving the claimed invention.

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

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[690] *Id.*

[691] *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).

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

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

The proposed combinations do not render the independent claims of the '728 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[693]

With respect to Claims 8 and 19, Defendants contend, without support, that "[a]s there is no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without increasing LDL-C, in this manner, with a reasonable expectation of success." Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[694] These contentions are inadequate to establish *prima facie* obviousness.

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a

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[693] *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").

[694] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[695] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[696] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[697] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[698]

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

[696] 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).

[697] *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).

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

Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively. Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.[699] Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient population*, and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[700] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[701] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[702]

The analysis of the independent claims of the '728 Patent is incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active

[699] *See* Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

[700] *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").

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

[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").

Ingredient in Lovaza with EPA of the Recited Composition

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '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.

characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[704] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C.

Further, Satoh was a small study conducted in only Japanese patients. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[705] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

[704] Defendants' Joint Invalidity Contentions at 205-06.

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

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[706] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[707] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[708] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki and/or Contacos.

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[709] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

[706] Defendants' Joint Invalidity Contentions at 205-06.

[707] Shinozaki at 107-109.

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

[709] Defendants' Joint Invalidity Contentions at 209.

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

Defendants rely on Geppert and/or Kelley to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[710] Both Geppert and Kelley administer DHA-rich oil that contained other saturated and polyunsaturated fatty acids. Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[711]

[710] Defendants' Joint Invalidity Contentions at 207.

[711] *See* Mori 2006 at 96.

For example, Defendants' own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.[712]

In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[713] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA was the only component of fish oil to increase LDL-C. For example, there is no data comparing DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying explain the mechanism of LDL-C increase.[714] A person of ordinary skill would have not expected that EPA and DHA would have different effects on LDL-C based on Geppert.

Defendants contend that Kelley shows that DHA was responsible for the increase in LDL-C.[715] In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon

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[712] Maki at 197.

[713] Geppert at 784.

[714] *Id*.

[715] Defendants' Joint Invalidity Contentions at 207.

associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[716] Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in context with the other lipid effects reported in the study. Kelley states that:

> DHA supplementation may lower the risk of CVD by reducing plasma triacylglycerols; triaclyglycerol:HDL; the number of small, dense LDL particles; and mean diameter of VLDL particles. An increase was observed in fasting LDL cholesterol, but it is unlikely this increase is detrimental because no increase was observed in the overall number of LDL particles; actually, there was an 11% reduction that was statistically not significant. The reason LDL cholesterol increased despite no change in LDL particle number was that the LDL particles were made larger and hence more cholesterol rich by DHA treatment.[717]

Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Kelley's ultimate conclusion is that "[o]verall, DHA supplementation reduced the concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins" and that "DHA supplementation may improve cardiovascular health."[718] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with negative attributes, a person of ordinary skill would understand that the reference taught towards the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy,

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[716] Kelley at 329.

[717] Kelley at 329

[718] Kelley at 324, 332.

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

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

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[719] As is the case with Kelley, Defendants use hindsight to characterize a reference based on LDL-C levels alone without considering the other lipid effects studied, considered and reported.[720] The isolated manner in which Defendants select such data points is not the approach that a person of ordinary skill would have taken at the time of the invention. Defendants' approach represents the use of impermissible hindsight bias. A person of ordinary skill would take into consideration the entire disclosure of a reference, including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a favorable effect in hypertriglyceridemic patients.

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

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

[720] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean diameters of these particles in fasting and postprandial plasma.").

without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[721] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert and/or Kelley.

(iv) A Person of Ordinary Skill Would Not Have Been Motivated to Find an Omega-3 Fatty Acid "therapy that would reduce TG levels in patients with TG levels ≥500 mg/dL without negatively impacting LDL-C levels."

Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[722] Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an

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

[722] *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).

LDL-C lowering medication such as a statin.[723] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[724] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[725] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

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

| | LDL-C Effect | |
|---|---|---|
| | Borderline-High or High TG Patients | Very-High TG Patients |
| Fibrate[726] | -20% | +45% |
| Lovaza/Omacor[727] | -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

[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 often required to achieve LDL-C and non-HDL-C goals");

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

[725] *See Id.*, ¶ 17

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

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

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."[728] 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.[729]

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[730] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when

[728] Defendants' Joint Invalidity Contentions at 208.

[729] *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

[730] 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")

discussing the TG-lowering mechanism of omega-3 fatty acids.[731] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels the most in patients with the highest pretreatment TG levels.[732] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-C was often offset by concurrent treatment with statins.[733] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[734]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[735] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[736]

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[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)

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

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

[734] McKenney at 722-23.

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

[736] *See* Pownall at 295 (stating that "[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by chancing LDL structure; lowering serum [cholesteryl ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C"); Harris 1997 at 389 (stating that "[t]he increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however," and "the use of omega-3 fatty acids for the

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[737] Correspondingly, prescription omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[738] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the number of small, dense LDL particles to larger LDL particles.[739] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[740] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not only for the

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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)").

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

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

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

[740] Stalenhoef at 134.

short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[741]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[742] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels. Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[743] (which is a reflection of total atherogenic

[741] Harris 1997 at 389.

[742] Defendants' Joint Invalidity Contentions at 208.

[743] *see* Section V.O.

lipoproteins)[744] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention.[745] Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population,[746] they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill would have understood these patient populations to be distinct with different impacts of lipid therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would not have considered the dosage modification suggested by defendants to be routine; Defendants' argument to the contrary represents hindsight bias.

[744] *see* Section III.

[745] *See, e.g.*, Defendants' Joint Invalidity Contentions at 197, 204-205.

[746]Defendants' Joint Invalidity Contentions at 236.

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

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

Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by combining the references cited by defendants. For a particular combination of references, there must be a reasonable expectation that the combination will produce the claimed invention. In this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG levels.[747] 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

[747] 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.

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[748] | -20% | +45% |
| Lovaza/Omacor[749] | -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.[750]

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating purified EPA to patients with very high triglyceride levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel.[751] Epadel was available for many years prior to the invention of the '728 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.

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

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

[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.

[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.

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

Defendants argue that because Grimsgaard administered purified ethyl EPA to patients with borderline-high/high TG, it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.[752] Defendants' contentions are no more than a demonstration that certain claim elements was known in the prior art and demonstrates impermissible hindsight reconstruction.[753] As is reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA, EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably,

[752] Defendants' Joint Invalidity Contentions at 210-11.

[753] *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.").

none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

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

| | DHA ($n$ = 72) | | EPA ($n$ = 75) | | Corn oil ($n$ = 77) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P^1$ | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[3] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[3] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

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

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

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

To the extent that Defendants' arguments are based on results that are not statistically significant and not reported by Grimsgaard as significant, a person of ordinary skill would not

draw conclusions from these statistically insignificant differences. Indeed, the standard deviation for the changes reported is greater than the value of the change itself.

Defendants argue that it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. However, the Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[754] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[755] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

Defendants argue that a person of ordinary skill at the time of the invention, based on studies in normal, borderline-high and high TG patients, knew that administration of DHA alone resulted in undesirable increased LDL-C levels while administration of EPA alone had little to no impact on LDL-C levels.[756] However, that statement does not conform with what was known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor were both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

With the lack of any reasonable expectation of success, Defendants argue that their proposed combination amounts to a simple substitution of one known element for another, and

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

[755] *See supra* Section III.

[756] Defendants' Joint Invalidity Contentions at 210.

that that these changes yield predictable results.[757] Such an argument, however, represents pure and impermissible hindsight bias and further does not consider that reasons for which a person of ordinary skill would not be motivated to combine these references and affirmatives ways in which the art taught away from these combinations.

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

(i) The '728 Patent is not Obvious Over WO '118 or WO '900, in Combination with the Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '728 Patent, Defendants present a combination of five references: "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."[758] Defendants also present charts arguing that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 61 separate references, they additionally do not identify any motivation for combining these references. [759, 760] Although Defendants need not point to an explicit statement

[757] Defendants' Joint Invalidity Contentions at 211.

[758] Defendants' Joint Invalidity Contentions at 213.

[759] Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor" similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 213.

[760] 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

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.[761] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[762] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[763] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the

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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 203-04.

[761] *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).

[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 any explanation as to how or why the references would be combined to produce the claimed invention").

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

risk of the cardiovascular events."[764] Contrary to Defendants' assertion that WO '118 discloses "the administration of 4 g of pure EPA with no DHA,"[765] WO '118 fails to disclose the claimed subject with the specified very high TG levels (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[766]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[767] WO '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[768]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[769] WO '118 states that

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[764] WO '118 at 9.

[765] Defendants' Joint Invalidity Contentions at 213.

[766] WO '118 at 22-23.

[767] WO '118 at 8.

[768] *See* Section III.

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

"[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[770] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[771] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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

WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[772] Moreover, WO '900 does not teach the desired effect of EPA other than commenting generally that it "may promote health and ameliorate or even reverse the effects of a range of common diseases."[773] It has no discussion, for example, on any TG-lowering effect of EPA.

[770] WO '118 at 22-23.

[771] WO '118 at 23.

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

[773] '900 Pub. at 5.

Although WO '900 identifies DHA as an "undesired molecule", it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than commenting generally that "the desired effects of EPA may be limited or reversed" by them.[774] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claims of the '728 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[775]

With respect to Claims 8 and 19, Defendants contend, without support, that "[a]s there is no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without increasing LDL-C, in this manner, with a reasonable expectation of success." Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[776] These contentions are inadequate to establish *prima facie* obviousness.

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[774] '900 Pub. at 39.

[775] *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").

[776] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[777] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[778] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying

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

[778] 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).

prior art references that purportedly disclose disparate elements.[779] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[780]

Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively. Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.[781] Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient population*, and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[782] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[783] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[784]

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[779] *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).

[780] *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.").

[781] *See* Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

[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.*, *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").

The analysis of the independent claims of the '728 patent is incorporated into all asserted claims that depend from those Claims.

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[785]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent reason" to combine must find a basis in the factual record.[786] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[787] Defendants' contentions are no more than an assertion that certain claim elements were known in

[785] Defendants' Joint Invalidity Contentions at 214.

[786] *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).

[787] *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").

the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[788] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '728 Patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000

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

and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in View of Katayama, Matsuzawa and/or Takaku.

With respect to the '728 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."[789] 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.[790] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[791] Defendants' contentions are no more than an assertion

[789] Defendants' Joint Invalidity Contentions at 214.

[790] *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).

[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").

that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[792] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900 , Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[793] 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

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

[793] Defendants' Joint Invalidity Contentions at 214.

record.[794] Defendants' assertions related to motivation are insufficient,[795] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[796] or "a reasonable expectation of success"[797] of achieving the claimed invention. Therefore, Defendants should be precluded from relying on this these references.

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

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[794] *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).

[795] For example, Defendants' assertion that "WO '118 may be combined with other prior art in the field of treating hypertriglyceridemia" is nothing more than a statement that a reference can be combined but fails to provide any basis for that statement. While the paragraph associated with that statement makes assertions regarding the disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO '118. *See* Defendants' Joint Invalidity Contentions at 214.

[796] *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).

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

serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population and do not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. As discussed above in Section V.A.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[798] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[799]

The proposed combination does not render the independent claims of the '728 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[800]

With respect to Claims 8 and 19, Defendants contend, without support, that "[a]s there is no significance attached to the 15% [or 5%] reduction of triglycerides . . . it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 15% [or 5%] without increasing LDL-C, in this manner, with a reasonable expectation of success." Defendants further

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[798] Takaku at ICOSAPENT_DFNDT00006897.

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

[800] *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").

contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[801] These contentions are inadequate to establish *prima facie* obviousness.

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[802] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[803] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

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[801] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

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

[803] 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).

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[804] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[805]

Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively. Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.[806] Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient population*, and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[807] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other

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[804] *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).

[805] *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.").

[806] *See* Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

[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").

disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[808] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[809]

The analysis of the independent claims of the '728 patent is incorporated into all asserted claims that depend from those Claims.

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

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[810]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.A.3.c.1.a.ii.a.iii is incorporated herein by reference. A person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not

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

[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.

disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[811] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[812] However, one of ordinary skill in the art knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[813] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[814] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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[811] Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

[812] Maki at 195.

[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 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.").

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

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

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[815] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides *without increasing LDL-C levels*.

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

| | LDL-C Effect | |
|---|---|---|
| | Borderline-High or High TG Patients | Very-High TG Patients |
| Fibrate[816] | -20% | +45% |
| Lovaza/Omacor[817] | -6% | +45% |

[815] Defendants' Joint Invalidity Contentions at 215.

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

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

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

Defendants further argue that the disclosure in WO '118 would combine with the prior art concerning Lovaza for at least two reasons; first, "products containing DHA were reported to increase LDL-C levels while products containing only EPA did not," and second, "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA."[818] Both of the "reasons" identified by Defendants are false.

Regarding Defendants' first reason, that "products containing DHA were reported to increase LDL-C levels while products containing only EPA did not," most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[819] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease,

[818] Defendants' Joint Invalidity Contentions at 215.

[819] Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

while EPA does not."[820] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[821] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that contained other saturated and polyunsaturated fatty acids.[822] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[823] Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[824] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[825] Finally, Theobald also does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when

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[820] Defendants' Joint Invalidity Contentions at 220.

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

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

[823] *See* Mori 2006 at 96.

[824] Kelley at 329.

[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.")

compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid.[826] Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[827] Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[828] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[829] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA," the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been

[826] Theobald at 560.

[827] *See* Mori 2006 at 96.

[828] Defendants' Joint Invalidity Contentions at 215.

[829] Mori 2000 at 1092.

well documented.[830] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[831] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[832] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[833]

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."[834] As discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[835]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that

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[830] 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.

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

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

[833] Harris 2008 at 13.

[834] Defendants' Joint Invalidity Contentions at 216.

[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").

DHA is *more* cardioprotective than EPA.[836] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[837] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[838] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[839] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA *and* DHA were known to have cardioprotective effects, and there were studies suggesting DHA was *more* cardioprotective than EPA.

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[840] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free,

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[836] Harris 2007 at 8.

[837] *Id.*

[838] Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 ("Low DHA was the most common finding across all studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.").

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

[840] Defendants' Joint Invalidity Contentions at 217.

highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[841]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[842] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[843] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG levels > 500 mg/dL."[844],[845] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one

[841] Defendants' Joint Invalidity Contentions at 217.

[842] *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.").

[843] Nakamura, Matsuzawa, and Takaku.

[844] Defendants' Joint Invalidity Contentions at 217.

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

patient had a baseline TG level > 500 mg/dL.[846] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[847] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[848] Based on this disclosure, only one patient definitively had a baseline TG level ≥ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[849] In Takaku, three patients had baseline TG levels above 500 mg/dL.[850] However, the mean baseline TG level for all patients was 245 mg/dL.[851] Indeed, the mean baseline TG level of the patients in all three studies was well below 500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[852] Defendants have failed to identify all of the claimed elements and fail to provide motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

[846] Nakamura at 23, Table 1.

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

[848] *Id.* at 23.

[849] *Id.* at 10.

[850] Takaku at ICOSAPENT_DFNDTS00006895.

[851] Takaku at ICOSAPENT_DFNDTS00006875.

[852] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[853] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[854] In fact, Defendants acknowledge in their Joint Invalidity Contentions that "DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[855] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[856] Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

[853] Defendants' Joint Invalidity Contentions at 218.

[854] Mori 2006 at 98.

[855] Defendants' Joint Invalidity Contentions at 222.

[856] Mori 2000 (showing that EPA reduced triglyceride by 18% while DHA reduced triglyceride by 20%); Rambjor (showing that fish oil reduced triglyceride more than EPA); Grimsgaard (showing that decrease in triglyceride was grater with DHA supplementation than EPA supplementation).

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[857] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[858] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia, because these studies were not designed to determine the effect of dose on the degree of TG reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[859] Therefore, a person of ordinary skill would not have been motivated to

[857] Defendants' Joint Invalidity Contentions at 218.

[858] Defendants' Joint Invalidity Contentions at 218.

[859] *See* Section III.

administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito treated subjects having baseline triglyceride levels greater than 500 mg/dl."[860] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500 mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy."[861] Defendants first support this argument by asserting that a person of ordinary skill in the art would have known that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA

[860] Defendants' Joint Invalidity Contentions at 218.

[861] Defendants' Joint Invalidity Contentions at 219.

to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition,[862] however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[863]

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

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[864] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[865]

Defendants rely on Kelley and the Lovaza label to argue that one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in

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[862] Defendants' Joint Invalidity Contentions at 219-20.

[863] *See* Section IV.

[864] Defendants' Joint Invalidity Contentions at 221.

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

LDL-C with DHA."[866] However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[867] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[868] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[869] (which is a reflection of total atherogenic lipoproteins) [870] in very high TG patients, and accordingly would not have been motivated to administer the claimed EPA composition to the very high TG patient population.

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

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[866] Defendants' Joint Invalidity Contentions at 222.

[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").

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

[869] *see* Section V.O.

[870] *see* Section III.

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

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[871] Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo."[872] However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of reducing triglycerides in a subject having very-high triglyceride levels by administering purified EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore, Defendants fail to provide a reasonable expectation of success for the claimed invention.

Defendants further argue, that "because it was known that DHA and EPA were comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition with a reasonable expectation of success that such administration would result in reducing triglycerides while avoiding an increase in LDL."[873] Defendants argument is without any basis.

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[871] Defendants' Joint Invalidity Contentions at 215.

[872] Defendants' Joint Invalidity Contentions at 219.

[873] Defendants' Joint Invalidity Contentions at 223.

To the contrary, because a person of ordinary skill in the art would have understood DHA and EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no explanation and cite to no article to support their argument that the similar effects on TG levels is a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected *both* EPA and DHA, whether administered alone or in combination, would cause an increase in LDL-C when administered to the very high TG patient population.

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but caused significant increases in LDL-C levels for patients with very-high triglycerides. The art cited by Defendants provides no basis for a person of ordinary skill to expect anything to the contrary. A person of ordinary skill would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as reflected in the prior art:

| | LDL-C Effect | |
|---|---|---|
| | Borderline-High or High TG Patients | Very-High TG Patients |
| Fibrate[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).

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

Defendants' position that a person of ordinary skill would have had a reasonable expectation of success in administrating purified EPA to the requisite patient population to achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel, which was available for many years prior to the invention of the '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.

(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

combined to teach the administration of the claimed EPA to very high TG patients.[876] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[877] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[878]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[879]

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

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[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").

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

[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").

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

purpose.[880] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(b) Defendants Have Not Shown that Claims 4 and 11 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1, 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 4 and 11.

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.[881] 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

[880] *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.")

[881] *Id.*

conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be combined.[882] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[883] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each prior art reference as a whole.[884] Each reference must be evaluated for all that it teaches. Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[885]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed methods of treatment, without providing a reason that would have prompted a person of ordinary

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[882] *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").

[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").

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

[885] *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").

skill to combine the elements.[886] Such a naked assertion does not show why a person of ordinary skill would have been motivated to treat the recited patient population using the claimed methods of treatment.[887]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[888] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(c) Defendants Have Not Shown that Claims 5 and 12 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1, 8 and 19 in Section V.A.3. Because Defendants have not shown the obviousness of Claims 1 and 8 by

[886] *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)

[887] *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)).

[888] *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.")

clear and convincing evidence, they also have not adequately proven the obviousness of Claims 5 and 12.

Defendants contend that EPA is known to reduce non-HDL-C and VLDL-C levels. Defendants further contend that a person of ordinary skill would have a reasonable expectation that a composition comprising EPA, but not DHA, would lower non-HDL-C levels, citing a laundry list of references without explaining how each reference relates to the claimed invention.[889] These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[890] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[891] Defendants selectively cite to an unspecified isolated

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[889] *Id.*

[890] *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").

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

disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[892] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[893]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[894] As such, Defendants fail to demonstrate that there was no motivation to combine the references to achieve the claimed invention.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that a person of ordinary skill "would have a reasonable expectation that a composition comprising EPA, but not DHA would lower non-HDL-C levels," without providing a support other than simply identifying prior art references that purportedly disclose disparate elements.[895] The mere fact

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

[893] *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").

[894] *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)).

[895] *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

that elements are capable of being physically combined does not establish reasonable expectation of success.[896] What is more, Defendants do not even discuss the reasonable expectation of reducing non-HDL-C and VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of reducing non-HDL-C and VLDL-C levels using the claimed methods.

(d) Defendants Have Not Shown that Claims 6 and 13 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1, 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 6 and 13.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[897] 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

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to support the legal conclusion of obviousness.") (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted).

[896] *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.").

[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 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

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

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[898] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[899] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[900] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[901]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a

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[898] *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").

[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").

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

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

conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[902] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[903] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[904] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[905]

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

[903] 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).

[904] *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).

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

(e) Defendants Have Not Shown that Claims 7 and 14 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1, 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 7 and 14. Claims 7 and 14 additionally include the claim element of administering to the subject about 4g of the claimed pharmaceutical composition for a period of 12 weeks to effect a reduction in fasting Lp-PLA2 of at least 10% compared to the second subject.

Defendants' contentions fail to disclose each and every element of the claims of the '560 patent. Specifically, Defendants do not contend that the relied upon references disclose the following element of Claim 7: *administering the claimed pharmaceutical composition to the recited subject to effect a reduction in fasting Lp-PLA2 of at least 10% compared to the second subject*. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Defendants contend that "Virani discloses the correlation between Lp-PLA2 and Apo-B," and that Zalewski discloses that Lp-PL2 co-travels with LDL. Defendants then conclude, without support, that "one of ordinary skill in the art would expect that the claimed methods would reduce Apo-B, discussed above, and would therefore also reduce Lp-PLA2 with a reasonable expectation of success." Defendants further contend that "given the correlation between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to reduce Lp-PLA2 to therapeutic levels. . . [and] [a]s there is no significance provided by the patentee regarding the various percentage reductions of Lp-PLA2, it would have been obvious" to a person of ordinary skill to seek to reduce Lp-PLA2 by 5% and 15%, with reasonable

expectation of success.[906] These contentions: 1) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Virani, Zalewski and Shinozaki do not render Claims 7 or 14 obvious. None of the references disclose or suggest the administration of the claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 10%.

Virani and Zalewski are both general review articles that discuss Lp-PLA2's biological role in atherosclerosis. Virani reviews the potential mechanisms by which Lp-PLA2 may "participate in the pathogenesis of atherosclerosis and its clinical manifestations, namely, coronary artery disease and stroke."[907] Zalewski is a highly technical review of the biological role of Lp-PLA2 in atherosclerosis. Neither article suggests or even discusses the administration of any omega-3 fatty acid and any possible effects on Lp-PLA2 that may result. Defendants have failed to identify even a single a prior art reference that discloses the administration of the claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 10%. Defendants fail to provide a basis for their assertion that "one of ordinary skill in the art would expect that the claimed methods would reduce Apo-B, discussed above, and would therefore also reduce Lp-PLA2 with a reasonable expectation of success." As discussed in Section V.O, a

[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."

[907] Virani at 97.

person of ordinary skill in the art did *not* expect that the claimed method would reduce Apo-B. Defendants have failed to prove that a decrease in Apo-B would lead a person of ordinary skill in the art to expect that Lp-PLA2 would also decrease simply because "Lp-PLA2 circulates bound to LDL via Apolipoprotein B." Defendants have further failed to meet their burden as they do no articulate an "apparent reason" to combine the elements in the manner claimed,[908] or offer an argument related to "a reasonable expectation of success."[909]

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Shinozaki does not discuss Lp-PLA2. In fact, Defendants rely on portions of Shinozaki that discuss effects of EPA administration on TG, total cholesterol, and lipoprotein (a) levels. Accordingly, Shinozaki does not disclose or suggest the administration of the claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 10%.

Defendants do not provide any basis for their assertion that "given the correlation between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to reduce Lp-PLA2 levels to therapeutic levels." Such an assertion does not provide any evidence of motivation or reasonable expectation of success in achieving the claimed invention, including the reduction in fasting Lp-PLA2 of at least 10%. Further, while Virani discloses that statins and

[908] *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).

[909] *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).

fibrates decrease Lp-PLA2, there is no mention of the use of omega-3 fatty acids.[910] Virani and Zalewski disclose that further research needs to be conducted regarding the relationship between Lp-PLA2 and atherosclerosis.[911]

Defendants fail to provide any factual basis to support their allegation of obviousness and reasonable expectation of success. Accordingly claims 7 and 14 of the '728 Patent are not obvious in light of Virani, Zalewski and/or Shinozaki.

(f) Defendants Have Not Shown that Claims 15 and 17 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1, 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 15 and 17.

Defendants contend that it would be obvious to use the claimed methods to treat patients who consume a Western diet, because cardiovascular disease is a leading cause of death in the United States and most European countries, and because it was common practice to advise patients receiving triglyceride-lowering treatments to maintain their diet. 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

[910] Virani at 101.

[911] Virani at 101 ("Understanding the role of Lp-PLA2 provides further insights into the process of atherosclerosis 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.").

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

Defendants do not identify any combination of references and simply provide a list of references that purportedly disclose disparate elements without explaining how they can be combined.[912] Defendants offer no support or explanation for their assertion that "it is a well-known, common practice to advise patients receiving triglyceride-lowering treatments to maintain their diet." As an initial matter, Defendants' assertion—even if true—does not support their obviousness claim and Defendants do not explain the connection between "maintain[ing]" diet and the asserted claim. Defendants offer a laundry list of citations that do not appear to support their unexplained assertion. Further, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[913] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[914] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[915]

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[912] *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").

[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").

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

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

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants merely state that the cardiovascular disease is a leading cause of death in the United States and most European countries, and do not explain how that would have prompted a person of ordinary skill to use the claimed method to treat patients who consume a Western diet.[916]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[917] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(g) Defendants Have Not Shown that Claims 16 and 18 of the '728 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claims 1, 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, it also has not adequately proven the obviousness of Claims 16 and 18.

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[916] *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)).

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

Defendants contend that WO '900 discloses EPA purity of over 90%, including 96%, and that it teaches the desirability of excluding other fatty acid substances from the composition, including DHA. Defendants further contend that the claims are obvious because "patentees have not provided any explanation of significance relating to the 0.6% by weight value." These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[918] Defendants fail to cite a single reference that discloses administration of the claimed EPA with no more than 0.6% of any fatty acid, other than EPA, to treat patients. Nor do Defendant explain how the cited reference can be combined with other references to achieve the claimed invention.[919] As such, Defendants discuss the claim elements in isolation, and fail to

[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").

[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").

address the claimed invention as a whole.[920] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[921] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[922]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants merely state that WO '900 teaches the desirability of excluding other fatty acid substances from the composition, and do not explain how that would have prompted a person of ordinary skill to limit the fatty acid content of fatty acids other than EPA to no more than 0.6% by weight of all fatty acids combined.[923] In fact, WO '900 does not teach the specific undesired of effect of the impurities, or to what extent the impurity content should be limited. Moreover, Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance"

[920] *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").

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

[922] *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").

[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)).

attached to the recited impurity limit.[924] Defendants have not met the burden with the naked assertion that the claims are obvious.[925]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[926] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

**4. The '728 Patent is Not Invalid Under § 112**

a) Defendants Have Not Provided Demonstrated that the Claims of the '728 Patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[927] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the

[924] 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).

[925] *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)

[926] *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.")

[927] 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.

art about the scope of the invention" in light of the specification and the prosecution history.[928] The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[929]

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[930] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[931] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[932] Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

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

[929] *Id.* at 2129.

[930] *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.").

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

[932] *See generally* the '728 patent and its prosecution history.

Defendants further allege that the terms "4g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate" and "wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined" are indefinite. They contend that, because there is no indication of how much of the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[933] In light of the specification and prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[934] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants further allege that the term "who does not receive concurrent lipid altering therapy" is indefinite. Defendants provide no basis for this allegation. In light of the specification and the prosecution history, however, a person of ordinary skill in the art would understand with reasonable certainty the scope of a "concurrent lipid altering therapy."[935]

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[933] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. Mar. 5, 2012) (construing "by weight" to mean the weight of a first component was in a ratio to the weight of a second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27, 2011) (construing percent by weight to mean "ratio of the weight of the ingredient in question divided by the total volume of the solution, with this ratio expressed as a percentage").

[934] *See generally* the '728 patent and its prosecution history.

[935] *See generally* the '728 patent and its prosecution history.

Moreover, lipid altering therapies are discussed in the patent specification.[936] Therefore, the phrase "concurrent lipid altering therapy" does not render the claim indefinite.

Defendants further allege that the term "consume a Western diet" is indefinite because it is "too vague." But the specification and the prosecution history describe (and even define) a "Western diet."[937] In light of the specification and the prosecution history, a person of ordinary skill would know with reasonable certainty the scope of the term "Western diet," and therefore the term does not render the claims indefinite.

Defendants also allege that it is impossible to ascertain the metes and bounds of "compared to . . . a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl …." A person of ordinary skill, however, would understand the metes and bounds of the term in light of the specification and the prosecution history.[938] Moreover, the method of comparing a subject to a second subject, such as a placebo controlled, randomized, double blind study, would have been known to a person of ordinary skill at the time of the invention. Therefore, the term does not render the claims indefinite.

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be

[936] See e.g., '728 patent at 12:43-46; 13:66-5.

[937] *See generally* the '728 patent and its prosecution history; see e.g., '728 patent at 9:24-38.

[938] *See generally* the '728 patent and its prosecution history.

asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent."[939] Plaintiffs assert that Defendants' ANDA products will be used in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '728 patent claims are not indefinite for improperly mixing methods and formulations.

b) Defendants Have Not Demonstrated that the Claims of the '728 Patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" to a skilled artisan that the applicant "invented" or "had possession" of the claimed subject matter when the application was filed.[940] Support need not be literal[941]—it may be implicit[942] or inherent[943] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[944]

Defendants make three arguments regarding the written description requirement. First, 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).

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

[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).

[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.

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

[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.

written description. This is incorrect. The specification of asserted patents literally discloses the claimed invention.[945] Moreover, the recited baseline TG levels of the claimed invention appear in the original claims of the application to which the asserted patent claims priority. Thus, there is a strong presumption that the claimed invention is adequately described.[946] Defendants do not and cannot rebut this presumption. Specifically, the patient population is originally claimed as "a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl."[947] The asserted claims recite the same patient population. Defendants do not contend that the patient population of the asserted claims is not literally described by the specification and in the original claims of the application to which the asserted patent claims priority. In fact, the specification and the provisional patent application claims at the time of filing describe these limitations.[948] Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the

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

[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 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").

[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.

dosages and quantities of the claimed methods.[949] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[950] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[951] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against a second subject or against a second population." The specification demonstrates that the applicants were in possession of the claimed inventions. For example, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a comparison of a subject or a population against a second subject or a second population.

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

[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 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").

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

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[952] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[953] Written description requires only that the specification reasonably conveys that the applicant had possession of the claimed subject matter when the application was filed. Therefore, whether the claims are obvious has no bearing on the adequacy of written description.

c) Defendants Have Not Demonstrated that the Claims of the '728 Patent Are Invalid for Lack of Enablement

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

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

[953] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (. 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.").

Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[954] The enablement requirement is separate and distinct from the written description requirement,[955] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[956]

Defendants make three specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary skill would be able to determine the amounts of the components in the pharmaceutical composition without any experimentation, much less undue experimentation.

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The

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

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

[956] MPEP § 2164.

clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[957] Therefore, the claims are not invalid for lack of enablement.

Third, Defendants allege that "it would require undue experimentation to obtain the claimed required results in subjects who do 'not receive concurrent lipid altering therapy' because the patentee did not separately study such subjects." Yet, as Defendants admit, the example in the specification includes both subjects who did not receive concurrent lipid altering therapy. This is consistent with the prosecution history, which includes a study of both subjects on statins and not on statins.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '728 patent's specification enables a person of ordinary skill to obtain the claimed limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.A.3. Furthermore, Plaintiffs have initiated human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its

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

claimed methods.[958,959] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

B. **The '715 Patent**

**1. The '715 Patent Claims Eligible Subject Matter Under § 101**

Defendants' allegation that the asserted claims of the '715 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[960] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '715 patent does not meet this requirement and thwarts the purpose of the Rules.[961]

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical

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

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

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

[961] Nor does the preceding paragraph, which provides only a purported summary of the claims of the '715 patent, or subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. *See, e.g.*, *Silver State Intellectual Techs., Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) ("The District of Nevada's Local Patent Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those contentions when new information comes to light in the course of discovery") (internal quotation marks omitted).

phenomenon, or abstract idea.[962] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[963]

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '715 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and] conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[964] However, the claims merely recited this natural law without reciting any novel application of it.[965] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[966] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[967]

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions

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[962] *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.").

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

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

[965] *Id.* at 1301.

[966] *Id.*

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

make clear that EPA of the requisite purity and characteristics is not found in nature.[968] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their natural state are patent-eligible.[969] Moreover, Defendants' assertions are immaterial to a Section 101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[970]

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[971] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[972] To say that the claims of the '715 patent claim a law of nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to

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[968] *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).

[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).

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

[971] *See* Defendants' Joint Invalidity Contentions at 248.

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

underlying principles of nature" that would "make all inventions unpatentable."[973] Indeed, even those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[974]

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '715 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[975] As discussed above, the asserted claims of the '715 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[976]

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

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

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

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

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

### 2. The Asserted Claims of the '715 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[977] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.[978] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[979] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[980] In addition, public "possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[981] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[982] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[983]

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

[978] *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).

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

[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).

[981] *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).

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

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

Defendants assert that Claims 1-19 of the '715 Patent are anticipated by the WO '118 reference.[984]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference into Exhibit B, and vice-versa. WO '118 does not anticipate the claims of the '715 patent because it does not describe, properly arrange, or enable the '715 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '715 Patent

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

It is well established that, for a prior art reference to anticipate, "every element of the claimed invention must be identically shown in a single reference."[985] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[986] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '715 Patent: *to effect a reduction in triglycerides and apolipoprotein B in the subject compared to a triglyceride level and apolipoprotein B level in a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, and who has not received the pharmaceutical composition*. WO '118 entirely fails to disclose the following elements of Claim 13 of the '715 Patent: *to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein*

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[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.

[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).

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

*B in the subject.* WO '118 entirely fails to disclose the following elements of Claim 17 of the '715 Patent: *to effect reduction in triglycerides and apolipoprotein B in the subject compared to a triglyceride level and an apolipoprotein B level at a baseline prior to initial administration of the pharmaceutical composition.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[987] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claims of the '715 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid

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

effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[988] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[989] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[990] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claims every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[991] Rambjor is a clinical study which administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

Therefore, WO '118 cannot anticipate the independent claims of the '715 patent. Because the dependent claims include all of the claim elements of the independent claims, WO' 118 cannot anticipate any of the dependent claims as well.

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

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

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

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

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

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

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[992] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[993]

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

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[994] The recitation of a "method of reducing

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

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

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

triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[995] Thus, the entire preamble in the independent claims of the '715 must contain patentable weight.

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

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina."[996] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[997] WO '118 does not

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

[996] WO '118 at 12.

[997] *Id.*

expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claims.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of the reference.[998] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

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

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

used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[999] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claims every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '715 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[1000] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1001] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as

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

[1000] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[1001] *Atofina*, 441 F.3d at 1000.

compared to the patent's claimed range of 0.1 to 5.0 percent.[1002] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1003] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[1004] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[1005] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL),

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[1002] *Id.*

[1003] *Id.*

[1004] *See* Section III.

[1005] *Id.*

and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[1006] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[1007] Accordingly, in these populations, physicians focused on lowering LDL-C.[1008] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary treatment goal.[1009] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claims of the '715 Patent.

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[1006] ATP III at 3335; *See also* Section III.

[1007] *Id.*

[1008] *Id.*

[1009] *Id.*

Third, WO '118 fails to disclose the claim element of "a subject . . . who does not receive a concurrent lipid altering therapy." Defendants' only basis for concluding that WO '118 teaches this element is that WO '118 "discloses and claims the administration of EPA-E without the administration in combination with statins."[1010] This sentence appears to be incomplete, as it is unclear what Defendants mean by "without the administration in combination with statins." This single statement, without citation to a single page in WO '118, fails to demonstrate that WO '118 teaches this element. In fact, WO '118 methods comprise statins, i.e. HMG-CoA RI.[1011]

WO '118 states that its disclosed composition is "effective in preventing occurrence of cardiovascular events in hypercholesterolemia patients, and **in particular**, in preventing occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[1012] WO '118 goes on to state that the "effect of the composition of the present invention will be synergistically improved by combined use with the HMG-CoA RI, and such use of the composition of the present invention with the HMG-CoA RI has clinical utility since the effect of preventing the cardiovascular event occurrence is expected to be improved."[1013] Administering the composition of WO '118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-CoA RI has on the disclosed compound. Further, WO '118 teaches that the disclosed composition may be used with a long list of other drugs, including lipid altering drugs such as antilipotropic drugs and fibrate drugs.[1014] Thus, WO '118 does not disclose administration of the

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[1010] Defendants' Invalidity Contentions at 46.

[1011] HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

[1012] WO '118 at 9 (emphasis added).

[1013] *Id.* at 10.

[1014] *Id.* at 24-25.

claimed EPA compositions to a subject that has very high TG levels and also "does not receive a concurrent lipid altering therapy" and cannot anticipate the independent claims of the '715 patent. In fact, the example of the methods of WO '118 expressly teaches a statin/EPA co-therapy. Because the dependent claims depend from the independent claims, they include the elements of the independent claims. Thus, WO '118 cannot anticipate any of the dependent claims of the '715 patent.

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

WO '118 further does not anticipate the claims of the '715 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '715 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less

one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1015] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[1016] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1017] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '715 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '715 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '715 patent and cannot anticipate the independent claims of the '715 Patent.

WO '118 further does not anticipate the claims of the '715 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a

[1015] *Atofina*, 441 F.3d at 1000.

[1016] *Id.*

[1017] *Id.*

portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[1018] Therefore, WO '118 discloses EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed generic range for the EPA composition in the claimed pharmaceutical composition.

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[1019] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1020] and therefore failed to anticipate the claimed range.[1021] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[1022] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to

[1018] WO '118 at 22.

[1019] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[1020] *Atofina*, 441 F.3d at 1000.

[1021] *Atofina*, 441 F.3d at 1000.

[1022] *Id.*

anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1023]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '715 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '715 patent. Therefore, WO '118's broad disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claims of the '715 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[1024] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '715 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between. There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claims of the '715 patent.

[1023] *Id.*

[1024] WO '118 at 22.

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

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

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

Defendants fail to address any of the claim elements of the dependent claims. Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any meaningful basis for concluding that WO '118 teaches these elements. Defendants further argue that "aspects of the claims relating to effects that are to be achieved by practicing the claimed method represent inherent, natural properties of EPA, and are entitled to no patentable weight." To the extent the recited claim elements relate to the administration step,

the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method, Defendants' contentions that the claim limitations are inherent properties of EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO '118, they fail to identify any basis, explanation, or even supporting argument for that assertion. Defendants have not met the burden to establish anticipation with the naked assertion that the effects are inherent, natural properties of EPA.

Further, Defendants entirely fail to prove that inherently discloses the recited claim limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[1025] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[1026] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[1027] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

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[1025] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[1026] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[1027] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

### 3. The Claims of the '715 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '715 Patent obvious.[1028] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '715 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of the '715 Patent itself to guide its combination of references.[1029] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[1030]

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

- 1) ". . .the asserted claims of the '715 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos)."

- 2) ". . .the asserted claims of the '715 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of

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[1028] Defendants' Joint Invalidity Contentions at 13-25.

[1029] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

[1030] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to rely on undisclosed or insufficiently disclosed references or argument.

administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku, further in view of Nozaki and/or Hayashi and further in view of Grimsgaard, Mori 2000 and/or Maki."

- 3) ". . .the asserted claims of the '715 patent would have been obvious over Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos.

- 4) ". . . the asserted claims of the '715 patent would have been obvious over WO '118 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."

- 5) ". . . the asserted claims of the '715 patent would have been obvious over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[1031] 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.[1032]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[1033] Indeed, any teaching in the art that points away from the claimed invention must be considered.[1034] A reference teaches away if a person of ordinary skill, upon reading the reference, would be

[1031] 35 U.S.C. § 103(a).

[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).

[1033] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1034] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.[1035] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[1036]

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[1037] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[1038] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[1039]

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[1040] "[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."[1041] "This is so because inventions in most, if not all, instances rely upon building

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[1035] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[1036] *Id*.

[1037] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[1038] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[1039] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

[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))

blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[1042]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[1043] or to modify a prior art reference in a way that "would destroy the fundamental characteristics of that reference."[1044] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[1045] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[1046] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[1047]

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[1048] and "a reasonable expectation of success."[1049]

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[1042] *KSR*, 550 U.S. at 418-419.

[1043] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

[1044] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[1045] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[1046] *Id*. at 88.

[1047] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

[1048] *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).

[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).

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[1050] This protects against the use of hindsight to pick through the prior art based solely on structural similarity to the claimed compound.[1051] Any assertion of an "apparent reason" must find a basis in the factual record.[1052]

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[1053] including those discovered after the patent was filed or even issued.[1054] "The basic principle behind this rule is straight-forward—that which would

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[1050] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd*., 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

[1051] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co*., 840 F.2d 902, 907 (Fed. Cir. 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int'l., Ltd. v. Solutia, Inc*., 289 F.3d 1367, 1376 (Fed. Cir. 2002).

[1052] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[W]hile KSR relaxed some of the formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi Sankyo*, 619 F.3d at 1354 (The assertion of a starting point "must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and elements of the prior art compounds."); *Forest Labs.*, 438 F.Supp.2d at 492–93 (rejecting defendants' contention that claims to (+)-citalopram were "prima facie obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988").

[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. . . . [T]he ordinary medicinal chemist would not have expected famotidine to have the 'most desirable combination of pharmacological properties' that it possesses."); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 364 F.Supp.2d 820, 908 (S.D. Ind. 2005) ("[S]uccess was not simply finding a compound as active as clozapine . . . . Here, the ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of pharmacological properties that it possesses.").

[1054] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

have been surprising to a person of ordinary skill in a particular art would not have been obvious."[1055] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[1056]

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[1057] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[1058] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[1059] These factual inquiries "guard against slipping into use of hindsight,"[1060] and "may often be the most probative and cogent evidence of nonobviousness."[1061]

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[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.").

[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.'").

[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).

[1058] *Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1569 (Fed. Cir. 1987).

[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.

[1060] *Graham*, 383 U.S. at 36.

[1061] *Ortho-McNeil Pharm. Inc. v. Mylan Labs. Inc*., 520 F.3d 1358, 1365 (Fed. Cir. 2008) (*quoting Catalina Lighting Inc. v. Lamps Plus, Inc.*, 295 F.3d 1277, 1288 (Fed. Cir. 2002)).

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[1062]

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

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying concentrations, in a wide range of doses and administration periods, to subjects who have baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[1063] Inconsistency in dosages and administration periods

[1062] *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.").

[1063] Mori 2006 at 96.

and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[1064] Defendants mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[1065] In addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower

[1064] Defendants' Joint Invalidity Contentions at 260 (*see* n.36).

[1065] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been a few patients with TG> 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline TG values < 500 mg/dL).

TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[1066] Clinically, the authoritative guidance to physicians on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[1067]

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

[1066] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

[1067] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG level of the patient receiving treatment.

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[1068] The fibrate, Tricor (fenofibrate), for example, decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[1069] and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[1070] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[1071] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[1072] Similar results were seen with the administration of Lopid (gemfibrozil).[1073] The differing effects of fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with

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[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).

[1070] *Id.*

[1071] *Id. See also*, Trilipix Label at 27.

[1072] *Id. See also*, Trilipix Label at 27.

[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).

normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

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

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.[1075] It had no significant effect on other lipid-related variable, including LDL-C and Apo-B.[1076] 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%.[1077] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[1078]

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[1074] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[1075] Chan 2002 I at 2379-81.

[1076] *Id.; See also*, Westphal at 918.

[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.

[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

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[1079] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the

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

[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.").

highest baseline TG levels[1080] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '715 patent are inherent to the compound when administered to a human subject."[1081] Inherency may not supply a missing claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[1082] Obviousness is based on what is *known* in the art at the time of the invention.[1083] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[1084] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

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[1080] Bays 2008 I at 400-402.

[1081] Defendants' Joint Invalidity Contentions at 261.

[1082] *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).

[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.

Defendants argue that the claims of the '715 patent which contain "a limiting clause, such as 'to effect' or 'effecting,'" simply express the intended result of a process step positively recited and therefore are not elements.[1085] This is incorrect. "There is nothing inherently wrong with defining some part of an invention in functional terms."[1086] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[1087] The claim term "to effect" acts as a positive claim element if the term represents "unexpected and improved effects of administration of the claimed compound."[1088] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

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

Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent. Where a limitation is absent from any Independent Claim, that limitation is absent from all asserted claims, and that analysis is incorporated by reference into each dependent claim. For any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted claims is not a concession that such limitation is present in the reference. By discussing

[1085] Defendants' Joint Invalidity Contentions at 262.

[1086] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971 )).

[1087] Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

[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).

Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants have appropriately divided the claim language for any purpose.

(1) WO '118

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '715 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), WO '118 does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. WO '118 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or dosage. With respect to Claim 13, WO '118 further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, WO '118 further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl compared to the second subject. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject.

(2) WO '900

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '900 disclose or suggest elements of the '715 Claims. The cited portions of WO '900 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of WO '900 further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. WO '900 also does not disclose or

suggest the claimed pharmaceutical composition with the recited fatty acid dosage. With respect to Claim 13, WO '900 further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, WO '900 further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl compared to the second subject. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject.

(3) Contacos

Contacos describes a study designed to determine the safety and efficacy of a statin (pravastatin) combined with fish oil either alone or in combination, for the management of patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '715 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest administration

of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Contacos does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. With respect to Claim 13, Contacos further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Contacos further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claim 14, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject. With respect to

Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject.

(4) Grimsgaard

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of the '715 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or administration period. With respect to Claim 13, Grimsgaard further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically

significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Grimsgaard further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject.

(5) Hayashi

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

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '715 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject

had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or administration period. With respect to Claim 13, Hayashi further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Hayashi further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,

VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject.

(6) Katayama

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '715 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Katayama further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Katayama does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions dosage. With respect to Claim 13, Katayama further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Katayama further does not

disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(7) Leigh-Firbank

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '715 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition to

effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. With respect to Claim 13, Leigh-Firbank further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Leigh-Firbank further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. Further, with respect to Claim 14, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(8) Lovaza PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '715 Claims. The cited portions of the Lovaza PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. With respect to Claim 13, the Lovaza PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B. With respect to Claims 1 and 17, the Lovaza PDR further does not disclose or suggest a method of reducing apolipoprotein B.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels. With respect to Claim 14, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(9) Maki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '715 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Maki further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. With respect to Claim 13, Maki further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Maki further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. With respect to Claim 14, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(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 '715 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Matsuzawa further do not disclose or suggest 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 a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Matsuzawa does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Matsuzawa also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions dosage. With respect to Claim 13, Matsuzawa further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Matsuzawa further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. With respect to Claim 14, this reference fails to disclose or suggest a method the administration of the claimed pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(11) Mori 2000

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of the '715 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or administration period. With respect to Claim 13, Mori 2000 further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Mori 2000 further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C,

VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(12) Mori 2006

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '715 Claims. The cited portions of Mori 2006 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of Mori 2006 further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. With respect to Claim 13, Mori 2006 further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or

Apo-B in the subject. With respect to Claims 1 and 17, Mori 2006 further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. Further, with respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '715 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid

compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '715 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Nozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or administration period. With respect to Claim 13, Nozaki further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Nozaki further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject

having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject.

(14) Omacor PDR

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '715 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Omacor PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. With respect to Claim 13, the Omacor PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting

a statistically significant increase in LDL-C or Apo-B. With respect to Claims 1 and 17, the Omacor PDR further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. Further, with respect to Claim 14, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(15) Satoh

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '715 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or

dosage. The cited portions of Satoh further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or dosage. With respect to Claim 13, Satoh further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Satoh further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. Further, with respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(16) Shinozaki

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '715 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level.

With respect to Claim 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or dosage. With respect to Claim 13, Shinozaki further does not disclose or suggest a method to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject with the claimed TG level. With respect to Claims 1 and 17, Shinozaki further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject

having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. Further, with respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

(17) Takaku

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

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '715 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject.

With respect to Claims 1, 13, and 17 of the '715 Patent (and therefore all asserted claims), Takaku does not disclose or suggest a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Takaku also does not disclose or suggest the

claimed pharmaceutical composition with the recited fatty acid compositions dosage. With respect to Claim 13, Takaku further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect a statistically significant reduction in TG without effecting a statistically significant increase in LDL-C or Apo-B in the subject. With respect to Claims 1 and 17, Takaku further does not disclose or suggest a method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl.

Further, with respect to Claim 4, this reference fails to disclose or suggest a method to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl. With respect to Claims 5–10, this reference fails to disclose or suggest the recited triglyceride, non-HDL-C, VLDL-C, Lp-PLA2, total cholesterol effects in the subject with the claimed TG levels based on a comparison to the second subject. Further, with respect to Claim 14, this reference fails to disclose or suggest a method to effect a statistically significant reduction in TG and Apo-B without effecting a statistically significant increase in LDL-C in the subject with the claimed TG level. With respect to Claims 11, 15, and 18, this reference fails to disclose or suggest the subject and second subject consume a Western diet.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the ’715 Patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent

Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '715 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claims 1-19: (1) a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl *who does not receive concurrent lipid altering therapy*; or (2) administering the claimed pharmaceutical composition to the recited subject to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '715 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '715 Patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claims of the '715 Patent Would Have Been Obvious

(a) Defendants Do Not Demonstrate that a Person of Ordinary Skill in the Art Would Have Had Any Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

(i) The '715 Patent is not Obvious Over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000

(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 Invalidity 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, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald," similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 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 Invalidity 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*

represents hindsight reconstruction.[1093] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1094] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C or Apo-B. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. The Lovaza PDR does not disclose any Apo-B effects when Lovaza was administered to the very high TG patient population. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375

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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 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).

[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)

mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claims of the '715 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, Satoh, Shinozaki Contacos, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1095]

The analysis of the independent claims of the '715 Patent are incorporated into all asserted claims that depend from this Claim.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '715 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 effect a statistically significant reduction in TG levels without effecting a statistically significant increase in LDL-C or Apo-B levels.

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

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies

[1095] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.[1096] 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 '715 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[1097] This is an incorrect characterization

[1096] *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.)

[1097] Defendants' Joint Invalidity Contentions at 255.

of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[1098] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

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

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference

[1098] Defendants' Joint Invalidity Contentions at 255.

disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[1099] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[1100]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[1101] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[1102] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[1103] Katayama does not disclose *any* LDL-C related

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[1099] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of $PGI_2$ and $PGI_3$ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[1100] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[1101] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1102] Defendants' Joint Invalidity Contentions at 255.

[1103] Katayama at 2.

data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[1104] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[1105] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[1106] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

[1104] *Id.* at 16.

[1105] Defendants' Joint Invalidity Contentions at 255.

[1106] Matsuzawa at 7 and 19.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[1107] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[1108] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[1109] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with

[1107] *Id.* at 23.

[1108] *Id.* at 10.

[1109] *Id.* at 11.

triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[1110] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[1111] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '715 patent.

(ii) Nozaki or Hayashi Do Not Disclose Purported Known

[1110] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

[1111] *See, e.g.*, Rambjor.

Clinical Benefits of
Administering Pure EPA

Defendants contend that Nozaki and Hayashi disclose the purported known clinical benefit of administering pure EPA, lowering TGs "without raising Apolipoprotein B."[1112] Nozaki and Hayashi do not disclose or suggest "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B" when purified EPA is administered to the very high TG patient population as the claims of the '715 Patent require.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[1113] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and

[1112] Defendants' Joint Invalidity Contentions at 255-256.

[1113] Nozaki at 256.

substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject" as the claims of the '715 Patent require.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[1114] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject" as the claims of the '715 Patent require.

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

[1114] Hayashi at 26, Table I.

patient population is exclusively Japanese cannot be generalized to other populations.[1115] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

(iii) Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos) 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."[1116] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As

[1115] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1116] Defendants' Joint Invalidity Contentions at 258.

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

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which contained other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[1117] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid

[1117] Mori 2006 at 96.

parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[1118] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[1119] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."[1120] Although teaching away is fact-dependent, "in general, a reference will teach

[1118] Leigh-Firbank at 440.

[1119] *See, e.g.* Grimsgaard at 654.

[1120] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[1121]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[1122] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the $HDL_2$-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[1123] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[1124] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

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[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.").

[1122] Mori 2000 at 1092.

[1123] Mori 2000 at 1088.

[1124] Mori 2000 at 1092.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1125] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

Defendants purport to formulate an obviousness argument that relies on Satoh or Shinozaki in view of Contacos.[1126,1127] However, Defendants fail to provide any factual or legal basis as to why Satoh, Shinozaki, or Contacos disclose a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[1128] or "a reasonable expectation of success"[1129] of achieving the claimed invention.

Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and pravastatin, but it does not disclose administration of EPA of the recited composition. Contacos

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[1125] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[1126] Defendants' Joint Invalidity Contentions at 255.

[1127] Further, it is not apparent what combination or combinations of references Defendants assert in their purported obviousness argument based on "Lovaza PDR in combination with . . . Katayama and/or Matsuzawa, and further in view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos)." In failing to identify the role of "Satoh or Shinozaki in view of Contacos" in this purported obviousness combination or offer any associated explanation, they have failed to meet their contentions burden. Accordingly, defendants should be precluded from relying on this purported combination.

[1128] *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).

[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).

demonstrated that fish oil does not increase LDL-C or Apo-B when administered to patients. Contacos also fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C or Apo-B.

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.[1130] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. In addition, Satoh does not disclose the effect of EPA on Apo-B. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C or Apo-B.

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

[1130] Satoh at 145.

states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[1131] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Shinozaki says nothing about an LDL-C or Apo-B effect because it measured only LDL particle number and Lp(a), and did not measure LDL-C or Apo-B. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[1132] In addition to Shinozaki's lack of disclosure regarding LDL-C or Apo-B, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the "Lovaza PDR in combination with . . . Katayama and/or Matsuzawa, and further in view of Leigh-Firbank and/or Mori 2000 (and/or Satoh or Shinozaki in view of Contacos)."

(ii) The '715 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or

[1131] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1132] Shinozaki at 107-109.

Hayashi and Further in View of Grimsgaard, Mori 2000 and/or Maki

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").

claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1136] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '715 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1137]

The analysis of the independent claims of the '715 Patent is incorporated into all asserted claims that depend from this Claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to

[1136] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1137] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '715 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

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

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

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[1138] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

[1138] Defendants' Joint Invalidity Contentions at 259.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[1139] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[1140] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in LDL-C by EPA, as confirmation "that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels."[1141] 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

[1139] Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG levels. (*See* Grimsgaard at Abstract (describing participants as "healthy") and Table 4).

[1140] Grimsgaard at 654.

[1141] Defendants' Joint Invalidity 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) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P$[1] | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[3] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[5] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

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

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[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.

it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard as confirmation "that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[1144] A person of ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[1145] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[1146] based on long-term administration.[1147]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a

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[1144] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make such arguments for the obvious reason that it does not support their argument that EPA was known to have little or no impact on LDL-C levels.

[1145] Defendants' Joint Invalidity Contentions at 256.

[1146] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[1147] Takaku at ICOSAPENT_DFNDT00006834.

conclusion "only from the results of the present study."[1148] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[1149]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[1150] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[1151] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[1152] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other

[1148] Takaku at ICOSAPENT_DFNDT00006897.

[1149] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1150] Takaku at ICOSAPENT_DFNDT00006884.

[1151] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[1152] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

times.[1153] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[1154]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[1155] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[1156] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Defendants contend that Nozaki and Hayashi disclose the purported known clinical benefit of administering pure EPA, lowering TGs "without raising Apolipoprotein B."[1157]

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[1153] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[1154] Takaku at ICOSAPENT_DFNDT00006897.

[1155] Takaku at ICOSAPENT_DFNDT00006897.

[1156] *See, e.g.*, Rambjor.

[1157] Defendants' Joint Invalidity Contentions at 255.

Nozaki and Hayashi do not disclose or suggest "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B" when purified EPA is administered to the very high TG patient population as the claims of the '715 Patent require.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[1158] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject" as the claims of the '715 Patent require.

[1158] Nozaki at 256.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[1159] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject" as the claims of the '715 Patent require.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[1160] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6

[1159] Hayashi at 26, Table I.

[1160] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

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

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

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[1161] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or Maki —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from

[1161] Defendants' Joint Invalidity Contentions at 258.

a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[1162] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[1163] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with below-average levels of HDL-C levels.[1164] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated, monounsaturated and polyunsaturated fatty acids.[1165] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[1166] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have

[1162] Defendants' Joint Invalidity Contentions at 256.

[1163] Defendants' Joint Invalidity Contentions at 258-59.

[1164] Maki at 190.

[1165] Maki at 191.

[1166] Maki at 195.

also contributed to the elevation in LDL cholesterol."[1167] Further, Maki admits that the "mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[1168] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Defendants mischaracterize the rise in LDL-C associated with the administration of omega-3 fatty acids as being a "negative effect" because they incorrectly focus on only the LDL-C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in LDL-C to be troublesome; Maki states that "the lack of increase in the total/HDL cholesterol ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level less worrisome."[1169] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[1170]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1171] Defendants identify no other basis upon which a person of

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[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).

[1168] Maki at 197.

[1169] Maki at 197.

[1170] Maki at 197.

[1171] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(iii) The '715 Patent Is Not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or by Satoh or Shinozaki in Further View of Contacos

With respect to the '715 Patent, Defendants present a specific combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[1172] Defendants also present charts purporting to assert that an additional 60 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 60 separate references, they additionally do not suggest any identify for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent reason" to combine must find a basis in the factual record.[1173] Defendants' unsupported cobbling of selective disclosures

[1172] Defendants' Joint Invalidity Contentions at 256.

[1173] *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).

represents hindsight reconstruction.[1174] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1175] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants formulate an obviousness argument that relies on Contacos.[1176] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim

[1174] *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").

[1175] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1176] *Id.*

element, an "apparent reason" or motivation to combine the elements in the manner claimed,[1177] or "a reasonable expectation of success"[1178] of achieving the claimed invention.

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

The proposed combinations do not render the independent claims of the '715 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1179]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those

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[1177] *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).

[1178] *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).

[1179] *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").

references in order to achieve the invention of the claim as a whole. Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[1180] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[1181]

Defendants point to Leigh-Firbank as teaching that fish oils were known to reduce fasting TG levels by 25% and 34% in normolipidaemic and hyperlipidaemic groups, respectively. Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL.[1182] Leigh-Firbank fails to provide motivation to administer *purified EPA* to the *very high TG patient population*, and does not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. Defendants discuss the claim

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[1180] *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).

[1181] *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.").

[1182] *See* Section V.A.3.c.1.a.i.a.iii for further discussion related to Leigh-Firbank.

elements in isolation, and fail to address the claimed invention as a whole.[1183] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1184] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1185]

The analysis of the independent claims of the '715 Patent is incorporated into all asserted claims that depend from those Claims.

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

Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there was no motivation (or reasonable expectation of success) to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription

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[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").

[1184] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[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").

omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[1186] Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[1187] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[1188] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[1189] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

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

| | LDL-C Effect | |
|---|---|---|
| | Borderline-High or High TG Patients | Very-High TG Patients |

[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).

[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").

[1188] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[1189] *See Id.*, ¶ 17.

| | | |
|---|---|---|
| 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.

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[1194] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[1195] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels the most in patients with the highest pretreatment TG levels.[1196] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-C was often offset by concurrent treatment with statins.[1197] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[1198]

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[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").

[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)).

[1196] *See* Bays 2008 Rx Omega-3 p. 402.

[1197] *See* Harris 2008 at 14, McKenney at 722.

[1198] McKenney at 722-23.

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[1199] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[1200]

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[1201] Correspondingly, prescription omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[1202] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the

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[1199] *See* Westphal at 918, Harris 1997 at 389.

[1200] *See* Pownall at 295 (stating that "[t]reatment with ω-3 fatty acids appear to change the lipid profile of individuals with elevated TG to one that may be less atherogenic by chancing LDL structure; lowering serum [cholesteryl ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C"); Harris 1997 at 389 (stating that "[t]he increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however," and "the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD"); Bays III at 248 ("No clinical trial data exist that this rise in LDL-C represents harm or potential "toxicity" to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C)").

[1201] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

[1202] McKenney 2007 at 722 (*see* Fig. 1).

number of small, dense LDL particles to larger LDL particles.[1203] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[1204] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[1205]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[1206] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find

[1203] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[1204] Stalenhoef at 134.

[1205] Harris 1997 at 389.

[1206] Defendants' Joint Invalidity Contentions at 257-58.

a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention.[1207] Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population,[1208] they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill would have understood these patient populations to be distinct with different impacts of lipid therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would not have considered the dosage modification suggested by defendants to be routine; Defendants' argument to the contrary represents hindsight bias.

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

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[1207] *See, e.g.*, Defendants' Joint Invalidity Contentions at 253.

[1208] Defendants' Joint Invalidity 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 or ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides without substantially increasing LDL-C—by combining the references cited by defendants. For a particular combination of references, there must be a reasonable expectation that the combination will produce the claimed invention. In this case, the art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG levels.[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:

| | LDL-C Effect |
|---|---|

[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 administrating purified EPA to patients with very high triglyceride levels to achieve TG lowering without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel.[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.

levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides.

Defendants argue that because Grimsgaard administered purified ethyl EPA to patients with borderline-high/high TG, it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa.[1214] Defendants' contentions are no more than a demonstration that certain claim elements was known in the prior art and demonstrates impermissible hindsight reconstruction.[1215] As is reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA, EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably, none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

[1214] Defendants' Joint Invalidity Contentions at 260.

[1215] *See, e.g., Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that even under KSR, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.").

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

| | DHA ($n$ = 72) | | EPA ($n$ = 75) | | Corn oil ($n$ = 77) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P^1$ | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[5] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[3] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

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

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

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

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

Defendants argue that it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. However, the

Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[1216] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[1217] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

Defendants argue that a person of ordinary skill at the time of the invention, based on studies in normal, borderline-high and high TG patients, knew that administration of DHA alone resulted in undesirable increased LDL-C levels while administration of EPA alone had little to no impact on LDL-C levels.[1218] However, that statement does not conform with what was known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor were both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

Further, a person of ordinary skill in the art would have understood that EPA therapy would *not* reduce Apo-B[1219] (which is a reflection of total atherogenic lipoproteins) [1220] in very high TG patients, and accordingly would not have had a reasonable expectation of success in achieving the claimed invention (including its Apo-B effects) by administering the claimed EPA

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[1216] *See Sanofi*, 748 F.3d at 1360–61.

[1217] *See supra* Section III.

[1218] Defendants' Joint Invalidity Contentions at 259.

[1219] *see* Section V.O.

[1220] *see* Section III.

composition to the very high TG patient population. Indeed, Defendants assert that "as DHA was known to increase LDL-C, and as ApoB is a component of LDL-C, one of ordinary skill in the art would also reasonably expect that DHA causes an increase in ApoB."[1221] But Defendants provide no explanation as to why a person of ordinary skill in the art would reasonably expect EPA to differ from DHA and cause a reduction in ApoB.

With the lack of any reasonable expectation of success, Defendants argue that their proposed combination amounts to a simple substitution of one known element for another, and that that these changes yield predictable results.[1222] Such an argument, however, represents pure and impermissible hindsight bias and further does not consider that reasons for which a person of ordinary skill would not be motivated to combine these references and affirmatives ways in which the art taught away from these combinations.

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

(i) The '715 Patent is not Obvious Over WO '118 or WO '900, in Combination with the Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '715 Patent, Defendants present a combination of five references: "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."[1223] Defendants also present charts arguing that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill

[1221] Defendants' Joint Invalidity Contentions at 273.

[1222] Defendants' Joint Invalidity Contentions at 261.

[1223] Defendants' Joint Invalidity Contentions at 263.

would combine 61 separate references, they additionally do not identify any motivation for combining these references.[1224, 1225] 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.[1226] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1227] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other

[1224] Defendants' bare assertion that the asserted claims are obvious "in view of one or more the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor" similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 262.

[1225] 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 254.

[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").

disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1228] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[1229] Contrary to Defendants' assertion that WO '118 discloses "the administration of 4 g of pure EPA with no DHA,"[1230] WO '118 fails to disclose the claimed subject with the specified very high TG levels (500-1500 mg/dL) who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[1231]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[1232] WO

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[1228] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1229] WO '118 at 9.

[1230] Defendants' Joint Invalidity Contentions at 263.

[1231] WO '118 at 22-23.

[1232] WO '118 at 8.

'118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[1233]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[1234] WO '118 states that "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[1235] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[1236] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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

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[1233] *See* Section III.

[1234] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

[1235] WO '118 at 22-23.

[1236] WO '118 at 23.

WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[1237] Moreover, WO '900 does not teach the desired effect of EPA other than commenting generally that it "may promote health and ameliorate or even reverse the effects of a range of common diseases."[1238] It has no discussion, for example, on any TG-lowering effect of EPA. Although WO '900 identifies DHA as an "undesired molecule", it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than commenting generally that "the desired effects of EPA may be limited or reversed" by them.[1239] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claims of the '715 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1240]

The analysis of the independent claims of the '715 patent is incorporated into all asserted claims that depend from this Claim.

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

[1237] *See, e.g.*, '900 Pub. at 16-17.

[1238] '900 Pub. at 5.

[1239] '900 Pub. at 39.

[1240] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[1241]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent reason" to combine must find a basis in the factual record.[1242] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1243] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

[1241] Defendants' Joint Invalidity Contentions at 263.

[1242] *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).

[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").

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

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1244] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '715 Patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in

[1244] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

View of Katayama, Matsuzawa and/or Takaku.

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").

Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1248] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

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

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[1249] 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

[1248] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1249] Defendants' Joint Invalidity Contentions at 263.

record.[1250] Defendants' assertions related to motivation are insufficient,[1251] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed,[1252] or "a reasonable expectation of success"[1253] of achieving the claimed invention. Therefore, Defendants should be precluded from relying on this these references.

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

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[1250] *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).

[1251] For example, Defendants' assertion that "WO '118 may be combined with other prior art in the field of treating hypertriglyceridemia" is nothing more than a statement that a reference can be combined but fails to provide any basis for that statement. While the paragraph associated with that statement makes assertions regarding the disclosure of certain other references, it does not provide a basis for the assertion of motivation to combine with WO '118. *See* Defendants' Joint Invalidity Contentions at 264.

[1252] *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).

[1253] *Proctor & Gamble Co. v. Teva Pharms. USA, Inc*., 566 F.3d 989, 994 (Fed. Cir. 2009) (henceforth, "P&G"); *Takeda Chem. Indus. v. Alphapharm Pty., Ltd*., 492 F.3d 1350, 1361 (Fed. Cir. 2007); *KSR*, 550 U.S. at 416 (a combination of elements "must do more than yield a predictable result;" combining elements that work together "in an unexpected and fruitful manner" would not have been obvious).

serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population and do not provide any reasonable expectation of success in lowering TG levels in the very high TG patient population without increasing LDL-C. As discussed above in Section V.B.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[1254] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[1255]

The proposed combination does not render the independent claims of the '715 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1256]

The analysis of the independent claims of the '715 patent is incorporated into all asserted claims that depend from this Claim.

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

[1254] Takaku at ICOSAPENT_DFNDT00006897.

[1255] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[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").

Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[1257]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.B.3.c.1.a.ii.a.iii is incorporated herein by reference. A person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[1258] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is

[1257] Defendants' Joint Invalidity Contentions at 264.

[1258] Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[1259] However, one of ordinary skill in the art knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[1260] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1261] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

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

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[1262] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides

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[1259] Maki at 195.

[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.").

[1261] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[1262] Defendants' Joint Invalidity Contentions at 262.

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

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

| | LDL-C Effect | |
|---|---|---|
| | Borderline-High or High TG Patients | Very-High TG Patients |
| Fibrate[1263] | -20% | +45% |
| Lovaza/Omacor[1264] | -6% | +45% |

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

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

[1263] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[1264] Chan 2002 I at 2381 (Table 3).

increase LDL-C levels while products containing only EPA did not," and second, "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA."[1265] Both of the "reasons" identified by Defendants are false.

Regarding Defendants' first reason, that "products containing DHA were reported to increase LDL-C levels while products containing only EPA did not," most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[1266] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not."[1267] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[1268] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that contained other saturated and polyunsaturated fatty acids.[1269] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[1270] Kelley does not show that DHA is

[1265] Defendants' Joint Invalidity Contentions at 264-65.

[1266] Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

[1267] Defendants' Joint Invalidity Contentions at 269.

[1268] The discussion related to Leigh-Firbank in Section V.A.3.c.1.a.i.a.iii is incorporated herein by reference.

[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.

responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[1271] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[1272] Finally, Theobald also does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid. Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[1273]Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[1274] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after

[1271] Kelley at 329.

[1272] 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.")

[1273] *See* Mori 2006 at 96.

[1274] Defendants' Joint Invalidity Contentions at 264.

EPA supplementation."[1275] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA," the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been well documented.[1276] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[1277] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[1278] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[1279]

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[1275] Mori 2000 at 1092.

[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.

[1277] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[1278] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[1279] Harris 2008 at 13.

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."[1280] As discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[1281]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that DHA is *more* cardioprotective than EPA.[1282] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[1283] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[1284] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[1285] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA

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[1280] Defendants' Joint Invalidity Contentions at 265.

[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 and CHD risk.") ("Harris 2007").

[1282] Harris 2007 at 8.

[1283] *Id.*

[1284] Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 ("Low DHA was the most common finding across all studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.").

[1285] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs., Inc. v. Garlock*, Inc., 721 F.2d 1540, 1552 (Fed. Cir. 1983) ("[P]roceed[ing] contrary to the accepted wisdom of the prior art … is strong evidence of nonobviousness.").

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

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[1286] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[1287]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[1288] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[1289] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG

[1286] Defendants' Joint Invalidity Contentions at 267.

[1287] Defendants' Joint Invalidity Contentions at 267.

[1288] *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.").

[1289] Nakamura, Matsuzawa, and Takaku.

levels > 500 mg/dL."[1290],[1291] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one patient had a baseline TG level > 500 mg/dL.[1292] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[1293] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[1294] Based on this disclosure, only one patient definitively had a baseline TG level ≥ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[1295] In Takaku, three patients had baseline TG levels above 500 mg/dL.[1296] However, the mean baseline TG level for all patients was 245 mg/dL.[1297] Indeed, the mean baseline TG level of the patients in all three studies was well below

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[1290] Defendants' Joint Invalidity Contentions at 266.

[1291] Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

[1292] Nakamura at 23, Table 1.

[1293] Nakamura at 23, Tables 1 and 2.

[1294] *Id.* at 23.

[1295] *Id.* at 10.

[1296] Takaku at ICOSAPENT_DFNDTS00006895.

[1297] Takaku at ICOSAPENT_DFNDTS00006875.

500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[1298] Defendants have failed to identify all of the claimed elements and fail to provide motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[1299] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[1300] In fact, Defendants acknowledge in their Joint Invalidity Contentions that

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[1298] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

[1299] Defendants' Joint Invalidity Contentions at 267.

[1300] Mori 2006 at 98.

"DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[1301] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[1302] Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[1303] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[1304] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,

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[1301] Defendants' Joint Invalidity Contentions at 271.

[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 grater with DHA supplementation than EPA supplementation).

[1303] Defendants' Joint Invalidity Contentions at 267.

[1304] Defendants' Joint Invalidity Contentions at 268.

because these studies were not designed to determine the effect of dose on the degree of TG reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[1305] Therefore, a person of ordinary skill would not have been motivated to administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito 1998 treated subjects having baseline triglyceride levels greater than 500 mg/dl."[1306] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500 mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a

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[1305] *See* Section III.

[1306] Defendants' Joint Invalidity Contentions at 268.

reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy."[1307] Defendants first support this argument by asserting that a person of ordinary skill in the art would have known that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition,[1308] however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[1309]

Defendants next argue again that DHA was known to be responsible for the increase in LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of ordinary skill would understand that both EPA and DHA function similarly, and that both would have little to no impact on borderline-high TG patients in terms of LDL-C levels and would increase LDL-C levels in patients with very high TGs.

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[1310] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that

[1307] Defendants' Joint Invalidity Contentions at 269.

[1308] Defendants' Joint Invalidity Contentions at 269.

[1309] *See* Section IV.

[1310] Defendants' Joint Invalidity Contentions at 271.

the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[1311]

Defendants rely on Kelley and the Lovaza label to argue that "one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in LDL-C with DHA."[1312] However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[1313] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[1314] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

Accordingly, a person of ordinary skill would not have been motivated to combine WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not

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[1311] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride levels when given prescription omega-3 therapy"); Chan 2003.

[1312] Defendants' Joint Invalidity Contentions at 271.

[1313] 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").

[1314] Bays 2008 I, at 398; Bays *in* Kwiterovich at 247.

have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-Firbank and/or Mori 2000.

(iv) A Person of Ordinary Skill Would Not Have Had a Reasonable Expectation of Success with the Combinations Defendants Hypothesize

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[1315] Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo."[1316] However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of reducing triglycerides in a subject having very-high triglyceride levels by administering purified EPA to effect a reduction in triglycerides *without substantially increasing LDL-C*. Therefore, Defendants fail to provide a reasonable expectation of success for the claimed invention.

Defendants further argue, that "because it was known that DHA and EPA were comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition

[1315] Defendants' Joint Invalidity Contentions at 264.

[1316] Defendants' Joint Invalidity Contentions at 268.

with a reasonable expectation of success that such administration would result in reducing triglycerides while avoiding an increase in LDL."[1317] Defendants argument is without any basis. To the contrary, because a person of ordinary skill in the art would have understood DHA and EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no explanation and cite to no article to support their argument that the similar effects on TG levels is a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected *both* EPA and DHA, whether administered alone or in combination, would cause an increase in LDL-C when administered to the very high TG patient population.

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but 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 |
|---|---|

[1317] Defendants' Joint Invalidity Contentions at 272.

| | 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 administrating purified EPA to the requisite patient population to achieve a lowering in TG levels without substantially increasing LDL-C is belied by the fact that Defendants' provide no evidence that anyone thought to administer Epadel, which was available for many years prior to the invention of the '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).

Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides.

Accordingly, a person of ordinary skill would not have a reasonable expectation of success in achieving the claimed invention.

(2) Dependent Claims

(a) Defendants Have Not Shown that Claims 2, 3, 12, 16, and 19 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the independent claims in Section V.B.3. Because Defendants have not shown the obviousness of the independent claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 2, 3, 12, 16, and 19.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claims 2 and 3. Defendants contend, without providing any support, that the claim elements are the results of simply optimizing the conditions described in the prior art and within the purview of the skilled physicians. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. None of the cited references discloses administration of the claimed EPA to very high TG patients. Defendants further fail to explain how the cited references can be combined to teach the administration of the claimed EPA to very high TG patients.[1320] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1321] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1322]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[1323]

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, other than simply identifying prior art

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[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").

[1321] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[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").

[1323] *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)).

references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[1324] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(b) Defendants Have Not Shown that Claim 4 of the '715 Patent Would Have Been Obvious.

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.B.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 4.

Defendants offer no reference in support of their contention that this claim is obvious. Defendants contend, without providing any support, that it would be obvious to one of skill in the art to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also reduce LDL-C levels. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a 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.

[1324] *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.")

Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. None of the cited references discloses administration of the claimed EPA to very high TG patients. Defendants further fail to explain how the cited references can be combined to teach the administration of the claimed EPA to very high TG patients.[1325] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1326] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1327]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment would have been obvious but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[1328]

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[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").

[1326] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[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").

[1328] *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[1329] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

Defendants cite only one reference in their invalidity contentions with respect to this claim, Theobald, and *not* for the proposition that the asserted claim is obvious. Instead, Defendants cite Theobald for the proposition that "it was known that Apo-B is a component of LDL-C." Defendants cite to no passage or page of Theobald in connection with that argument and no support for their argument that Theobald makes such a disclosure. Defendants appear to suggest a correlation between Apo-B and LDL-C but ignore that Apo-B is present on all atherogenic lipoproteins.[1330]

Defendants then make the unsupported assertion that "one of ordinary skill in the art would reasonably expect that a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL syntheses." They are incorrect. Neither Defendants' characterization of Theobald nor the disclosures of that reference teach that EPA compositions would reduce Apo-B or render this claim obvious. Defendants' assertion that EPA was known to reduce VLDL synthesis ignores that, as discussed above, *see* Section III, DHA was also understood to reduce VLDL synthesis. Nor do defendants explain the relevance of VLDL synthesis to their arguments with respect to this claim or Apo-B levels.

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[1329] *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.")

[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 *Crypthecodinium cohnii* to healthy subjects. While Defendants make an unexplained citation to Theobald regarding the proposition that Apo-B is a component of LDL-C, they fail to discuss the reference's disclosures regarding the impact of administration of the triacylglycerol composition on Apo-B levels. In doing so, they fail to consider the reference for all that it teaches. Theobald discloses an *increase* in Apo-B following administration of the triacylglycerol composition of that reference:[1331]

**TABLE 3**
Serum lipoproteins before treatment and after 3 mo of docosahexaenoic acid (DHA) and placebo treatment in all subjects

| | DHA | | Placebo | | |
|---|---|---|---|---|---|
| | Before treatment | After treatment | Before treatment | After treatment | Treatment effect[1] |
| Total cholesterol (mmol/L) | 5.15 ± 0.145[2] | 5.44 ± 0.174 | 5.08 ± 0.168 | 5.22 ± 0.155 | 0.22 (0.01, 0.42)[3] |
| LDL cholesterol (mmol/L) | 3.16 ± 0.129 | 3.48 ± 0.152 | 3.16 ± 0.146 | 3.25 ± 0.131 | 0.23 (0.08, 0.38)[4] |
| HDL cholesterol (mmol/L)[5] | 1.47 ± 0.052 | 1.55 ± 0.064 | 1.46 ± 0.062 | 1.48 ± 0.056 | 0.07 (0.005, 0.14) |
| Triacylglycerol (mmol/L)[6] | 1.03 ± 0.094 | 1.01 ± 0.089 | 1.06 ± 0.106 | 1.19 ± 0.103 | −0.18 (−0.37, 0.05) |
| Apolipoprotein B (g/L) | 0.84 ± 0.027 | 0.87 ± 0.026 | 0.83 ± 0.028 | 0.84 ± 0.028 | 0.03 (0.002, 0.055)[7] |
| LDL cholesterol:apo B (mmol/g) | 3.75 ± 0.376 | 3.96 ± 0.462 | 3.74 ± 0.521 | 3.84 ± 0.409 | 0.12 (0.004, 0.24)[3] |
| Weight (kg)[8] | 70.1 ± 2.04 | 70.6 ± 2.06 | 70.5 ± 2.01 | 70.6 ± 2.01 | 0 (−0.85, 0.24) |

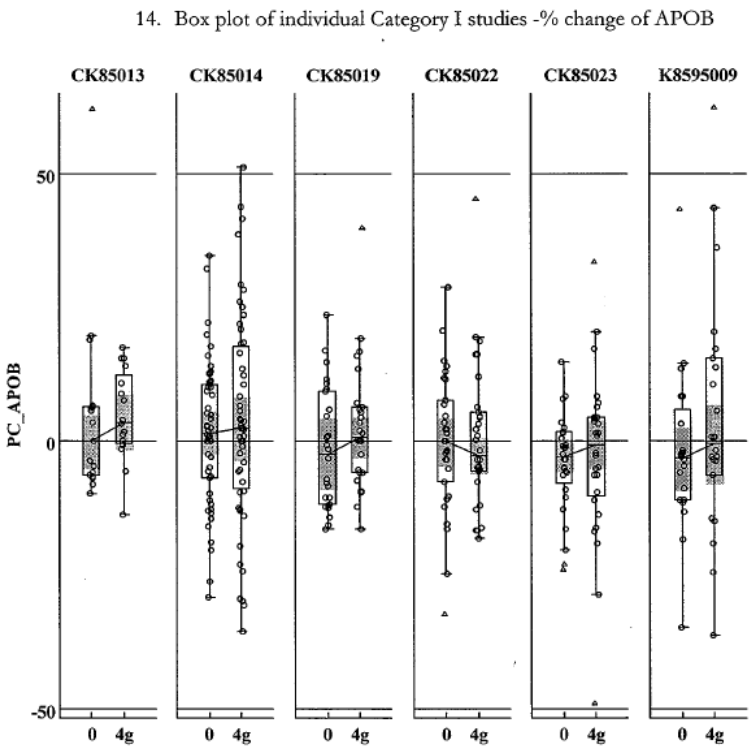
[1] Mean difference between active treatment and placebo; 95% CI in parentheses.
[2] $\bar{x}$ ± SEM (all such values); $n = 38$.
[3,4,7] Paired $t$ test: [3] $P = 0.04$, [4] $P = 0.004$, [7] $P = 0.03$.
[5] HDL increased in subjects receiving DHA first. Significant treatment × order effect, $P = 0.005$.
[6] $n = 37$; data were log transformed before analysis by paired $t$ test.
[8] Weight increased over the entire study period. Significant order × time effect, $P = 0.001$.

As discussed above, *see* Section III, a person of skill in the art would not have distinguished between the lipid effects of EPA and DHA therapy. To the extent, then that a person of ordinary skill would have considered Theobald, they would not conclude from the reference that EPA therapy decreases Apo-B levels in very high TG patients.

A person of skill in the art would *not* have understood that EPA therapy in very high TG patients would yield a reduction in Apo-B levels. A person of ordinary skill would have looked to the Lovaza clinical trials—the only clinical trial to study the effects of omega-3 fatty acids on

[1331] Theobald at 561, table 3.

Apo-B levels in patients with very high TG levels.[1332] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[1333]




In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[1334] 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.[1335]

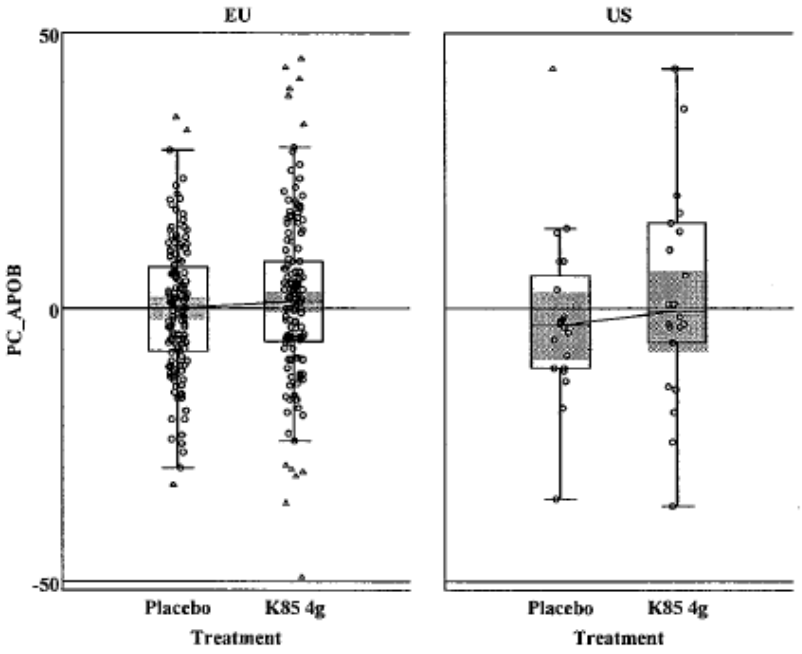
[1332] May 8, 2012 Bays Declaration.

[1333] Lovaza Approval Package at Table 14.

[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.

those references, also reflecting a lack of motivation and no reasonable expectation of success.[1337]

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[1338] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[1339] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

Accordingly, a person of ordinary skill in the art would not have been motivated to replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art have been motivated to administer the EPA composition of the claimed invention to very high TG patients. For the same reasons, a person of ordinary skill in the art would not have a reasonable expectation of success in achieving the claimed invention.

[1337] Defendants' Contentions at 236.

[1338] ATP-III at 3170; Bays 2008 I at 395.

[1339] Kwiterovich in Kwiterovich at 4.

(c) Defendants Have Not Shown that Claim 5 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the independent claims in Section V.B.3. Because Defendants have not shown the obviousness of Claim 1 by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 5.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[1340] 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.

[1340] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[1341] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1342] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1343] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1344]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[1345] Defendants' burden to

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[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").

[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").

[1343] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[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").

[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

establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[1346] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[1347] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[1348]

(d) Defendants Have Not Shown that Claims 6 and 7 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the independent claims in Section V.B.3. Because Defendants have not shown the obviousness of the independent claims

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claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

[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* case of obviousness by establishing that the claimed range is critical . . . .") (internal quotation marks omitted).

[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).

[1348] *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("[T]he 'predictable result' discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.").

by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 6 and 7.

Defendants contend that EPA is known to reduce non-HDL-C and VLDL-C levels. Defendants further contend that a person of ordinary skill would have a reasonable expectation that a composition comprising EPA, but not DHA, would lower non-HDL-C levels, citing a laundry list of references without explaining how each reference relates to the claimed invention.[1349] These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[1350] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1351] Defendants selectively cite to an unspecified isolated

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[1349] *Id.*

[1350] *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").

[1351] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008) ("The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim").

disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1352] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1353]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[1354] As such, Defendants fail to demonstrate that there was no motivation to combine the references to achieve the claimed invention.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that a person of ordinary skill "would have a reasonable expectation that a composition comprising EPA, but not DHA would lower non-HDL-C levels," without providing a support other than simply identifying prior art references that purportedly disclose disparate elements.[1355] The mere fact

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[1352] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1353] *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").

[1354] *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)).

[1355] *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

that elements are capable of being physically combined does not establish reasonable expectation of success.[1356] What is more, Defendants do not even discuss the reasonable expectation of reducing non-HDL-C and VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of reducing non-HDL-C and VLDL-C levels using the claimed methods.

(e) Defendants Have Not Shown that Claim 8 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the independent claims in Section V.B.3. Because Defendants have not shown the obviousness of the independent claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 8.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[1357] 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

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underpinning to support the legal conclusion of obviousness.") (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted).

[1356] *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.").

[1357] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[1358] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1359] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1360] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1361]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a

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[1358] *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").

[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").

[1360] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1361] *See, e.g.*, *Innogenetics N.V. v. Abbott Laboratories*, 512 F.3d 1363 (Fed. Cir. 2008) (noting that, even under *KSR*, "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention").

conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce triglycerides by 5% to 25%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[1362] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[1363] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element. In addition, Defendants have failed to provide any rationale for the assertion that there would be a reasonable expectation that a composition comprising EPA, but not DHA, would lower non-HDL-C levels." Defendants provide no explanation for this assertion and instead merely list numerous references.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying

[1362] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

[1363] 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).

prior art references that purportedly disclose disparate elements.[1364] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[1365]

(f) Defendants Have Not Shown that Claim 9 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to independent claim 1 in Section V.B.3. Because Defendants have not shown the obviousness of Claim 1 by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 9. Claim 9 additionally includes the claim element of administering to the subject about 4g of the claimed pharmaceutical composition for a period of 12 weeks to effect a reduction in fasting Lp-PLA2 of at least 15% compared to the second subject.

Defendants' contentions fail to disclose each and every element of the claims of the '715 patent. Specifically, Defendants do not contend that the relied upon references disclose the following element of Claim 9: *administering 4 g of the composition of the subject daily for a period of 12 weeks to effect a reduction in Lp-PLA2 of at least about 15% as compared to the Lp-PLA2 level in the second subject*. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Defendants contend that "Virani discloses the correlation between Lp-PLA2 and Apo-B," and that Zalewski discloses that Lp-PL2 co-travels with LDL. Defendants then conclude,

[1364] *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).

[1365] *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.").

without support, that "one of ordinary skill in the art would expect that the claimed methods would reduce Apo-B, discussed above, and would therefore also reduce Lp-PLA2 with a reasonable expectation of success." Defendants further contend that "given the correlation between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to reduce Lp-PLA2 to therapeutic levels. . . [and] [a]s there is no significance provided by the patentee regarding the various percentage reductions of Lp-PLA2, it would have been obvious" to a person of ordinary skill to seek to reduce Lp-PLA2 by 5% and 15%, with reasonable expectation of success.[1366] These contentions: 1) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 2) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Virani, Zalewski and Shinozaki do not render Claim 9 obvious. None of the references disclose or suggest the administration of the claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 15%.

Virani and Zalewski are both general review articles that discuss Lp-PLA2's biological role in atherosclerosis. Virani reviews the potential mechanisms by which Lp-PLA2 may "participate in the pathogenesis of atherosclerosis and its clinical manifestations, namely,

[1366] 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."

coronary artery disease and stroke."[1367] Zalewski is a highly technical review of the biological role of Lp-PLA2 in atherosclerosis. Neither article suggests or even discusses the administration of any omega-3 fatty acid and any possible effects on Lp-PLA2 that may result. Defendants have failed to identify even a single a prior art reference that discloses the administration of the claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 15%. Defendants fail to provide a basis for their assertion that "one of ordinary skill in the art would expect that the claimed methods would reduce Apo-B, discussed above, and would therefore also reduce Lp-PLA2 with a reasonable expectation of success." As discussed in Section V.O, a person of ordinary skill in the art did *not* expect that the claimed method would reduce Apo-B. Defendants have failed to prove that a decrease in Apo-B would lead a person of ordinary skill in the art to expect that Lp-PLA2 would also decrease simply because "Lp-PLA2 circulates bound to LDL via Apolipoprotein B." Defendants have further failed to meet their burden as they do no articulate an "apparent reason" to combine the elements in the manner claimed,[1368] or offer an argument related to "a reasonable expectation of success."[1369]

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Shinozaki does not discuss Lp-PLA2. In fact, Defendants rely on portions of Shinozaki that discuss effects of EPA administration on TG, total cholesterol, and lipoprotein (a) levels. Accordingly,

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[1367] Virani at 97.

[1368] *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).

[1369] *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).

Shinozaki does not disclose or suggest the administration of the claimed pharmaceutical compound to effect a reduction in fasting Lp-PLA2 of at least 15%.

Defendants do not provide any basis for their assertion that "given the correlation between Lp-PLA2 and cardiovascular disease, one of skill in the art would naturally seek to reduce Lp-PLA2 levels to therapeutic levels." Such an assertion does not provide any evidence of motivation or reasonable expectation of success in achieving the claimed invention, including the reduction in fasting Lp-PLA2 of at least 15%. Further, while Virani discloses that statins and fibrates decrease Lp-PLA2, there is no mention of the use of omega-3 fatty acids.[1370] Virani and Zalewski disclose that further research needs to be conducted regarding the relationship between Lp-PLA2 and atherosclerosis.[1371]

Defendants fail to provide any factual basis to support their allegation of obviousness and reasonable expectation of success. Accordingly claim 9 of the '715 Patent is not obvious in light of Virani, Zalewski and/or Shinozaki.

(g) Defendants Have Not Shown that Claim 10 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.B.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 10.

[1370] Virani at 101.

[1371] Virani at 101 ("Understanding the role of Lp-PLA2 provides further insights into the process of atherosclerosis 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.").

Defendants contend, without support, that a person of ordinary skill would naturally seek to reduce total cholesterol level because it represents therapeutic efficacy. Defendants further contend that recited percentage reductions of total cholesterol are obvious because there is no significance regarding the percentage reductions. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[1372] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1373] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a

[1372] *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").

[1373] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008) ("The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim").

whole. Each reference, however, must be evaluated for all that it teaches.[1374] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1375]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce total cholesterol by 5% to 15%," without providing a reason that would have prompted a person of ordinary skill to reduce total cholesterol by the recited amount.[1376] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited total cholesterol reduction amount.[1377] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claimed element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in

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[1374] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1375] *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").

[1376] *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)).

[1377] Plaintiffs do not have to show that a claimed range is critical unless a *prima facie* case of obviousness has been established. *See In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) ("An applicant may overcome a *prima facie* case of obviousness by establishing that the claimed range is critical . . . .") (internal quotation marks omitted).

achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[1378] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[1379]

(h) Defendants Have Not Shown that Claim 14 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claim in Section V.B.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 14.

Defendants' contentions fail to disclose each and every element of the claim 14 of the '715 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 14: (1) administering the claimed pharmaceutical composition to the recited subject to effect a statistically significant reduction in triglycerides *and* *Apolipoprotein B* without effecting a statistically significant increase in LDL-C in the subject. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Defendants contend, without support, that the recited reduction in TG represents therapeutic efficacy, and that a person of ordinary skill would naturally seek to reduce TG to

[1378] *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).

[1379] DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc., 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("[T]he 'predictable result' discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.").

therapeutic efficacy. Defendants further contend that it would have been obvious to a person of ordinary skill to seek to reduce TG by the recited amount because there is no significance attached to the amount. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention.[1380] These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references or any references that disclose any of the claim elements.[1381] Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily

[1380] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

[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 demonstrating that each of its elements was, independently, known in the prior art").

skilled artisan to seek to reduce triglycerides by, for example, 25% without increasing LDL-C by more than 5%," without providing a reason that would have prompted a person of ordinary skill to reduce triglycerides by the recited amount.[1382] Defendants fail to provide any argument related to motivation to effect a statistically significant reduction in Apo-B, as required by the claim. Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited TG reduction amount.[1383] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing any support.[1384] Defendants fail to provide any statement related to reasonable expectation of success of effecting a statistically significant

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[1382] *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) ("Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.") (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted); *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

[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).

reduction in Apo-B, as required by the claim. As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(i) Defendants Have Not Shown that Claims, 11, 15, and 18 of the '715 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.B.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 11, 15, and 17.

Defendants contend that it would be obvious to use the claimed methods to treat patients who consume a Western diet, because cardiovascular disease is a leading cause of death in the United States and most European countries, and because it was common practice to advise patients receiving triglyceride-lowering treatments to maintain their diet. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a list of references that purportedly disclose disparate elements without explaining how they can be

combined.[1385] Defendants offer no support or explanation for their assertion that "it is a well-known, common practice to advise patients receiving triglyceride-lowering treatments to maintain their diet." As an initial matter, Defendants' assertion—even if true—does not support their obviousness claim and Defendants do not explain the connection between "maintain[ing]" diet and the asserted claim. Defendants offer a laundry list of citations that do not appear to support their unexplained assertion. Further, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1386] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1387] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1388]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants merely state that the cardiovascular disease is a leading cause of death in the United States and most European

[1385] *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").

[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").

[1387] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1388] *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").

countries, and do not explain how that would have prompted a person of ordinary skill to use the claimed method to treat patients who consume a Western diet.[1389]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[1390] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

**4. The '715 Patent is Not Invalid Under § 112**

a) Defendants Have Not Demonstrated that the Claims of the '715 Patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[1391] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the

[1389] *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)).

[1390] *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.")

[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.

art about the scope of the invention" in light of the specification and the prosecution history.[1392] The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[1393]

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about," "substantially," and "statistically significant." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[1394] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[1395] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[1396] Therefore, the terms that contain the words "about," "substantially," and "statistically significant" are not invalid for being indefinite.

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[1392] *Nautilus, Inc. v. Biosig Instruments, Inc.*, 134 S. Ct. 2120, 2124 (2014).

[1393] *Id.* at 2129.

[1394] *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.").

[1395] *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).

[1396] *See generally* the '715 patent and its prosecution history.

Defendants further allege that the terms "a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate" and "wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined" are indefinite. They contend that, because there is no indication of how much of the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[1397] In light of the specification and prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[1398] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants further allege that the term "who does not receive concurrent lipid altering therapy" is indefinite. Defendants provide no basis for this allegation. In light of the specification and the prosecution history, however, a person of ordinary skill in the art would understand with reasonable certainty the scope of a "concurrent lipid altering therapy."[1399]

[1397] *T.F.H. Publications, Inc. v. Doskocil Mfg. Co.*, No. CIV.A. 08-4805 FLW, 2012 WL 715628, at *5–6 (D.N.J. Mar. 5, 2012) (construing "by weight" to mean the weight of a first component was in a ratio to the weight of a second component); *Allergan, Inc. v. Sandoz Inc.*, No. 2:09-CV-182, 2011 WL 1599049, at *10 (E.D. Tex. Apr. 27, 2011) (construing percent by weight to mean "ratio of the weight of the ingredient in question divided by the total volume of the solution, with this ratio expressed as a percentage").

[1398] *See generally* the '728 patent and its prosecution history.

[1399] *See generally* the '715 patent and its prosecution history.

Moreover, lipid altering therapies are discussed in the patent specification.[1400] Therefore, the phrase "concurrent lipid altering therapy" does not render the claim indefinite.

Defendants further allege that the term "consume a Western diet" is indefinite because it is "too vague." But the specification and the prosecution history describe (and even define) a "Western diet."[1401] In light of the specification and the prosecution history, a person of ordinary skill would know with reasonable certainty the scope of the term "Western diet" and therefore does not render the claims indefinite.

Defendants also allege that it is impossible to ascertain the metes and bounds of "compared to . . . a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl …." A person of ordinary skill, however, would understand the metes and bounds of the term in light of the specification and the prosecution history.[1402] Moreover, the method of comparing a subject to a second subject, such as a placebo controlled, randomized, double blind study, would have been known to a person of ordinary skill at the time of the invention. Therefore, the term does not render the claims indefinite.

Defendants further contend that the metes and bounds of the phrase "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject" is unclear. Defendants do not provide the basis for the assertion other than stating that it is unclear and the specification does not clarify its meaning. As discussed above, use of the phrase "statistically significant" does not render a claim *per se* indefinite. In light of the specification and the prosecution history, a person of ordinary skill in

[1400] See e.g., '715 patent at 12:43-46; 13:66-14:5.

[1401] *See generally* the '715 patent and its prosecution history.

[1402] *See generally* the '715 patent and its prosecution history.

the art would know with reasonable certainty the scope of the term "a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDL-C or Apolipoprotein B in the subject" and therefore does not render the claims indefinite.[1403]

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent."[1404] Plaintiffs assert that Defendants' ANDA products will be used in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '715 patent claims are not indefinite for improperly mixing methods and formulations.

Defendants argue that it is not clear who "the second subject" in Claim 18 is or why they must consume a Western diet. A person of ordinary skill in the art would understand that Claim 18 discloses a "The method of Claim 17 wherein the subject consumes a Western diet." This interpretation is not subject to reasonable debate based on consideration of the claim language and the specification and the prosecution history does not suggest a different interpretation of the

[1403] *See generally* the '715 patent and its prosecution history.

[1404] 35 U.S.C. § 271(c) (emphasis added).

claims. Also, the district court can retroactively correct certain errors in a patent's claims if "(1) the correction is not subject to reasonable debate based on consideration of the claim language and the specification and (2) the prosecution history does not suggest a different interpretation of the claims."[1405] In this case, any correction would be directed to an element that is not subject to reasonable debate and the prosecution history and specification do not suggest a contrary interpretation.

b) Defendants Have Not Demonstrated that the Claims of the '715 Patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" that the applicant "invented" or "had possession" of the claimed subject matter when the application was filed.[1406] Support need not be literal[1407]—it may be implicit[1408] or inherent[1409] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[1410]

Defendants make three arguments regarding the written description requirement. First, Defendants contend that elements reciting the baseline TG levels of the asserted claims lack

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[1405] *Novo Indus., L.P. v. Micro Molds Corp.*, 350 F.3d 1348, 1354, 1357 (Fed. Cir. 2003). These "determinations must be made from the point of view of one skilled in the art." *Ultimax Cement Mfg. v. CTS Cement Mfg.*, 587 F.3d 1339, 1353 (Fed. Cir. 2009).

[1406] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[1407] *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).

[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.

written description. This is incorrect. The specification of asserted patents literally discloses the claimed invention.[1411] Moreover, the recited baseline TG levels of the claimed invention appear in the original claims of the application to which the asserted patent claims priority. Thus, there is a strong presumption that the claimed invention is adequately described.[1412] Defendants do not and cannot rebut this presumption. Specifically, the patient population is originally claimed as "a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl."[1413] The asserted claims recite the same patient population. Defendants do not contend that the patient population of the asserted claims is not literally described by the specification and in the original claims of the application to which the asserted patent claims priority. In fact, the specification and the provisional patent application claims at the time of filing describe these limitations.[1414] Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the

[1411] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) ("[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."); *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) ("[T]he literal description of a species provides the requisite legal foundation for claiming that species.").

[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 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").

[1413] *See* U.S. Application No. 12/702,889.

[1414] See e.g., '715 patent at 13:29-34; 14:49-51; U.S. Application No. 12/702,889.

dosages and quantities of the claimed methods.[1415] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[1416] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[1417] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against a second subject or against a second population." The specification demonstrates that the applicants were in possession of the claimed inventions. For example, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a comparison of a subject or a population against a second subject or a second population.

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[1415] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) ("[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."); *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) ("[T]he literal description of a species provides the requisite legal foundation for claiming that species.").

[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 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.

Fourth, Defendants contend that "nowhere does the specification of the '715 patent describe or suggest comparing the effects of administering a composition in a subject against a second subject." The specification demonstrates that the inventors were in possession of a method of treating a patient with the claimed composition and having the claimed effects. Indeed, the claim limitations are stated in the specification. Moreover, an example with a clinical study protocol is disclosed.

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[1418] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[1419] Written description requires only that the specification reasonably conveys that the applicant had

[1418] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

[1419] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (. 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.").

possession of the claimed subject matter when the application was filed. Therefore, whether the claims are obvious has no bearing on the adequacy of written description.

c) Defendants Have Not Demonstrated that the Claims of the '715 Patent Are Invalid for Lack of Enablement

The first paragraph of 35 U.S.C. § 112 requires that the specification "enable any person skilled in the art . . . to make and use [the claimed invention]." A claim is not enabled if it would require undue experimentation for a person of ordinary skill to make or use the invention. Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[1420] The enablement requirement is separate and distinct from the written description requirement,[1421] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[1422]

Defendants make three specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary skill would be able to determine the amounts of the components in the pharmaceutical composition without any experimentation, much less undue experimentation.

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid

[1420] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[1421] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[1422] MPEP § 2164.

effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[1423] Therefore, the claims are not invalid for lack of enablement.

Third, Defendants allege that "it would require undue experimentation to obtain the claimed required results in subjects who do 'not receive concurrent lipid altering therapy' because the patentee did not separately study such subjects." Yet, as Defendants admit, the example in the specification includes both subjects who did not receive concurrent lipid altering therapy. This is consistent with the prosecution history, which includes a study of both subjects on statins and not on statins.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '715 patent's specification enables a person of ordinary skill to obtain the claimed

[1423] *See* VASCEPA Prescribing Information at Table 2.

limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.B.3. Furthermore, Plaintiffs have initiated human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its claimed methods.[1424, 1425] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

C. **The '335 Patent**

**1. The '335 Patent Claims Eligible Subject Matter Under § 101**

Defendants' allegation that the asserted claims of the '335 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[1426] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '335 patent does not meet this requirement and thwarts the purpose of the Rules.[1427]

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[1424] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.").

[1425] *See* May 16, 2011 Bays Declaration at Appendix B.

[1426] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[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

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical phenomenon, or abstract idea.[1428] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[1429]

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '335 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and] conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[1430] However, the claims merely recited this natural law without reciting any novel application of it.[1431] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[1432] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[1433]

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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).

[1428] *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.").

[1429] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

[1430] *Mayo*, 132 S. Ct. at 1294.

[1431] *Id.* at 1301.

[1432] *Id.*

[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

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions make clear that EPA of the requisite purity and characteristics is not found in nature.[1434] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their natural state are patent-eligible.[1435] Moreover, Defendants' assertions are immaterial to a Section 101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[1436]

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[1437] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[1438] To say that the claims of the '335 patent claim a law of

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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).

[1434] *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).

[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 (CCPA 1970); *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F.95 (S.D.N.Y. 1911).

[1436] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

[1437] *See* Defendants' Joint Invalidity 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

nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to underlying principles of nature" that would "make all inventions unpatentable."[1439] Indeed, even those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[1440]

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '335 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[1441] As discussed above, the asserted claims of the '335 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[1442]

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In

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to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin).").

[1439] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

[1440] *See Mayo*, 132 S. Ct. at 1034 ("Prometheus, supported by several *amici*, argues that a principle of law denying patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research.").

[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).

addition, as discussed above, the asserted claims are not merely a naturally-occurring phenomena, and thus satisfy the requirements of § 101.[1443]

### 2. The Asserted Claims of the '335 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[1444] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.[1445] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[1446] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[1447] In addition, public "possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[1448] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art,

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[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.").

[1444] *Akzo N.V. v. U.S. Int'l Trade Com'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986).

[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).

[1446] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[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).

[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).

and the breadth of the claims.[1449] This inquiry is objective, and thus evidence of undue experimentation need not be prior art.[1450]

Defendants assert that Claims 1-29 of the '335 Patent are anticipated by the WO '118 reference.[1451]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference into Exhibit C, and vice-versa. WO '118 does not anticipate the claims of the '335 patent because it does not describe, properly arrange, or enable the '335 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '335 Patent

(1) WO '118 Does Not Describe the Claimed Lipid Effects

It is well established that, for a prior art reference to anticipate, "every element of the claimed invention must be identically shown in a single reference."[1452] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[1453] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '335 Patent: *effective to reduce fasting triglycerides by at least about 15% compared to a fasting triglyceride level at a baseline prior to*

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[1449] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[1450] *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp*., 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc*., 449 F.3d 1209, 1224–25 (Fed. Cir. 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

[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.

[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).

[1453] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

*initial administration of the pharmaceutical composition.* WO '118 further entirely fails to disclose the following elements of Claim 14 of the '335 Patent: *effective to reduce fasting triglycerides by at least 25% and to reduce fasting Apolipoprotein B, compared to a second subject having a baseline triglyceride level of 500 mg/dl to about 2000 mg/dl who has not received the pharmaceutical composition and is not on concomitant statin therapy.* WO '118 also entirely fails to disclose the following elements of Claim 22 of the '335 Patent: *the subject exhibits a reduction in fasting triglycerides of at least about 25% and a reduction in fasting Apolipoprotein B compared to a control subject having a baseline triglyceride level of 500 mg/dl to about 2000 mg/dl who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[1454] Indeed, Defendants could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claims of the '335 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the

[1454] Defendants' Invalidity Contentions at 202-204.

claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[1455] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[1456] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[1457] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claims every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[1458] Rambjor is a clinical study which administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

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[1455] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[1456] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[1457] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[1458] *See, e.g.*, Rambjor.

Therefore, WO '118 cannot anticipate the independent claims of the '335 patent. Because the dependent claims include all of the claim elements of the independent claims, WO' 118 cannot anticipate any of the dependent claims as well.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[1459] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[1460]

The preamble of the asserted claims is limiting for several reasons. The term "subject" in the preamble of the independent claims defines and provides antecedent basis for the "subject" recited in the body of the claims. When reading the claim, one must rely on both the preamble and the claim body to define the claimed invention.

[1459] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

[1460] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[1461] The recitation of a "method of reducing triglycerides and Apolipoprotein B" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides and Apolipoprotein B.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[1462] Thus, the entire preamble in the independent claims of the '335 must contain patentable weight.

WO '118 fails to disclose the patentable elements of the preamble of the asserted claims. WO '118 does not describe or suggest that the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population.

First, WO '118 fails to expressly disclose "a method of reducing triglycerides." In fact, the invention disclosed by WO '118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads "Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient." The prevention of the occurrence of cardiovascular events is defined in WO '118 as "all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest

[1461] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases "portable computer" and "portable computer microprocessing system" limit the claims because they "clearly recite a necessary and defining aspect of the invention, specifically its portability," and because the specification and prosecution history "emphasize this feature of the invention").

[1462] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

angina and exercise-induced angina, and destabilization of the angina."[1463] The invention of WO '118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[1464] WO '118 does not expressly describe its invention as a "method of reducing triglycerides," therefore it cannot anticipate the independent claims.

Second, WO '118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have "strict identity" with the elements of the reference.[1465] WO '118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

There is no evidence in that subject as described in the claims were ever treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of the subject as described in the claims. It does not. Defendants' argument rests on the definition in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL." WO '118's definition is not tied to a specific subject and there are no working examples, data or other reference in WO '118 indicating that any subject with fasting TG levels of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as evidence that a "person of ordinary skill in the art would have understood that the term

[1463] WO '118 at 12.

[1464] *Id.*

[1465] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable and then merely provides examples of commercially available "soft capsules," such as Omacor. The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[1466] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claims every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '335 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between 330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[1467] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1468] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of

[1466] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[1467] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[1468] *Atofina*, 441 F.3d at 1000.

hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as compared to the patent's claimed range of 0.1 to 5.0 percent.[1469] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1470] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500 mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[1471] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500

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[1469] *Id.*

[1470] *Id.*

[1471] *See* Section III.

mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[1472] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL), and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[1473] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[1474] Accordingly, in these populations, physicians focused on lowering LDL-C.[1475] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary treatment goal.[1476] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular

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[1472] *Id.*

[1473] ATP III at 3335; *See also* Section III.

[1474] *Id.*

[1475] *Id.*

[1476] *Id.*

risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claims of the '335 Patent.

Third, WO '118 fails to disclose the claim element of "a subject . . . who is not on concomitant statin therapy," or "a subject . . . who is not on concurrent lipid altering therapy." Defendants' only basis for concluding that WO '118 teaches this element is that WO '118 "discloses and claims the administration of EPA-E without the administration in combination with statins."[1477] This sentence appears to be incomplete, as it is unclear what Defendants mean by "without the administration in combination with statins." This single statement, without citation to a single page in WO '118, fails to demonstrate that WO '118 teaches this element. In fact, WO '118 methods comprise statins, i.e. HMG-CoA RI.[1478]

WO '118 states that its disclosed composition is "effective in preventing occurrence of cardiovascular events in hypercholesterolemia patients, and **in particular**, in preventing occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[1479] WO '118 goes on to state that the "effect of the composition of the present invention will be synergistically improved by combined use with the HMG-CoA RI, and such use of the composition of the

[1477] Defendants' Invalidity Contentions at 46.

[1478] HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

[1479] WO '118 at 9 (emphasis added).

present invention with the HMG-CoA RI has clinical utility since the effect of preventing the cardiovascular event occurrence is expected to be improved."[1480] Administering the composition of WO '118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-CoA RI has on the disclosed compound. Further, WO '118 teaches that the disclosed composition may be used with a long list of other drugs, including lipid altering drugs such as antilipotropic drugs and fibrate drugs.[1481] Thus, WO '118 does not disclose administration of the claimed EPA compositions to a subject that has very high TG levels and also "not on concomitant statin therapy" or "not on concurrent lipid altering therapy" and cannot anticipate the independent claims of the '335 patent. In fact, the example of the methods of WO '118 expressly teaches a statin/EPA co-therapy. Because the dependent claims depend from the independent claims, they include the elements of the independent claims. Thus, WO '118 cannot anticipate any of the dependent claims of the '335 patent.

(3) WO '118 Does Not Describe the Claimed Pharmaceutical Composition or its Specific Administration

WO '118 further does not anticipate the claims of the '335 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '335 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more

[1480] *Id.* at 10.

[1481] *Id.* at 24-25.

preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1482] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[1483] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1484] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '335 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range

[1482] *Atofina*, 441 F.3d at 1000.

[1483] *Id.*

[1484] *Id.*

claimed by the '335 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '335 patent and cannot anticipate the independent claims of the '335 Patent.

WO '118 further does not anticipate the claims of the '335 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[1485] Therefore, WO '118 discloses EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed generic range for the EPA composition in the claimed pharmaceutical composition.

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[1486] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1487] and therefore failed

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[1485] WO '118 at 22.

[1486] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[1487] *Atofina*, 441 F.3d at 1000.

to anticipate the claimed range.[1488] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[1489] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1490]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '335 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '335 patent. Therefore, WO '118's broad disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claims of the '335 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[1491] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '335 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between.

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[1488] *Atofina*, 441 F.3d at 1000.

[1489] *Id.*

[1490] *Id.*

[1491] WO '118 at 22.

There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claims of the '335 patent.

Defendants contend that Plaintiffs are estopped from arguing there is any material difference between "not more than about 4% DHA" and "substantially no DHA." Defendants provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and Defendants have cited no authority to support their position suggesting the contrary. The language of "not more than about 4% DHA" and "substantially no DHA" are different phrases and are not co-extensive. Accordingly, plaintiffs are not estopped.

In the same paragraph containing their allegation of estoppel, Defendants also quote from Amarin's 2011 10-K. It is unclear whether these quotations are associated with their unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these statements form the basis for any theory of estoppel. To the extent that Defendants quote Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The quoted statements do not identify any recited claim element, including the specific pharmaceutical composition, the recited patient population, administration in the manner claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from the quoted statements.

(4) WO '118 Does Not Describe the Dependent Claims

Defendants fail to address any of the claim elements of the dependent claims. Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail

to set forth any meaningful basis for concluding that WO '118 teaches these elements. Defendants further argue that "aspects of the claims relating to effects that are to be achieved by practicing the claimed method represent inherent, natural properties of EPA, and are entitled to no patentable weight." To the extent the recited claim elements relate to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method, Defendants' contentions that the claim limitations are inherent properties of EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO '118, they fail to identify any basis, explanation, or even supporting argument for that assertion. Defendants have not met the burden to establish anticipation with the naked assertion that the effects are inherent, natural properties of EPA.

Further, Defendants entirely fail to prove that inherently discloses the recited claim limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[1492] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[1493] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[1494] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in

[1492] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[1493] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[1494] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

### 3. The Claims of the '335 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '335 patent obvious.[1495] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '335 patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of the '335 patent itself to guide its combination of references.[1496] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[1497]

Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions, Plaintiffs have discerned and will specifically respond to the following alleged prior art combinations:

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[1495] Defendants' Joint Invalidity Contentions at 13-25.

[1496] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

[1497] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to rely on undisclosed or insufficiently disclosed references or argument.

- 1) ". . .the asserted claims of the '335 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000."

- 2) ". . .the asserted claims of the '335 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."

- 3) ". . .the asserted claims of the '335 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '335 patent would have been obvious over WO '118 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."

- 5) ". . . the asserted claims of the '335 patent would have been obvious over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[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).

teaches, including the portions that would lead away from the claimed invention.[1500] Indeed, any teaching in the art that points away from the claimed invention must be considered.[1501] A reference teaches away if a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.[1502] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[1503]

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[1504] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[1505] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[1506]

"The determination of obviousness is made with respect to the subject matter as a whole,

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[1500] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1501] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

[1502] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[1503] *Id.*

[1504] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[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)

not separate pieces of the claim."[1507] "[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."[1508] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[1509]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[1510] or to modify a prior art reference in a way that "would destroy the fundamental characteristics of that reference."[1511] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[1512] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[1513] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[1514]

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[1507] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[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))

[1509] *KSR*, 550 U.S. at 418-419.

[1510] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

[1511] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[1512] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[1513] *Id*. at 88.

[1514] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[1515] and "a reasonable expectation of success."[1516]

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[1517] This protects against the use of hindsight to pick through the prior art based solely on structural similarity to the claimed compound.[1518] Any assertion of an "apparent reason" must find a basis in the factual record.[1519]

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[1515] *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).

[1516] *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).

[1517] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd*., 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

[1518] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co*., 840 F.2d 902, 907 (Fed. Cir. 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int'l., Ltd. v. Solutia, Inc*., 289 F.3d 1367, 1376 (Fed. Cir. 2002).

[1519] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[W]hile KSR relaxed some of the formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi Sankyo*, 619 F.3d at 1354 (The assertion of a starting point "must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and elements of the prior art compounds."); *Forest Labs.*, 438 F.Supp.2d at 492–93 (rejecting defendants' contention that claims to (+)-citalopram were "prima facie obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988").

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[1520] including those discovered after the patent was filed or even issued.[1521] "The basic principle behind this rule is straight-forward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[1522] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[1523]

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[1524] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[1525] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or

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[1520] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [T]he ordinary medicinal chemist would not have expected famotidine to have the 'most desirable combination of pharmacological properties' that it possesses."); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F.Supp.2d 820, 908 (S.D. Ind. 2005) ("[S]uccess was not simply finding a compound as active as clozapine . . . . Here, the ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of pharmacological properties that it possesses.").

[1521] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

[1522] *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.").

[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).

surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[1526] These factual inquiries "guard against slipping into use of hindsight,"[1527] and "may often be the most probative and cogent evidence of nonobviousness."[1528]

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[1529]

A element-by-element analysis, identifying each limitation of each asserted claim that is absent from the prior art, is provided below, and also provided at Exhibit C. The contentions below are incorporated by reference into Exhibit C, and vice-versa.

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying degrees of purity, in a wide range of doses and administration periods, to subjects who have

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[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 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.

[1527] *Graham*, 383 U.S. at 36.

[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)).

[1529] *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) ("[I]n order to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention."); *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968) ("[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public.").

baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[1530] Inconsistency in dosages and administration periods and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[1531] Defendants mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[1532] In

[1530] Mori 2006 at 96.

[1531] Defendants' Joint Invalidity Contentions at 484 (*see* FN 86).

[1532] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been a few patients with TG> 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline TG values < 500 mg/dL).

addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[1533] Clinically, the authoritative guidance to physicians on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by

[1533] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[1534]

Finally, from a therapeutic standpoint, a person of ordinary skill understood that the effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG level of the patient receiving treatment.

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[1535] The fibrate, Tricor (fenofibrate), for example, decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[1536] and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[1537] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[1538] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[1539] Similar results were seen with the administration of Lopid (gemfibrozil).[1540] The differing effects of

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[1534] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

[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).

[1536] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[1537] *Id.*

[1538] *Id. See also*, Trilipix Label at 27.

[1539] *Id. See also*, Trilipix Label at 27.

[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).

fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

| **Fibrate** | **Mean Baseline TG Value** | **TG** | **LDL-C** | **HDL-C** | **Total-C** |
|---|---|---|---|---|---|
| Tricor (fenofibrate)[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

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.[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.

B.[1543] 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%.[1544] Although the increase in LDL-C was concerning, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[1545]

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased

[1543] *Id.; See also*, Westphal at 918.

[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.

[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 [cholesteryl ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C."); Stalenhoef at 134 (stating that "Omacor . . . adversely raise LDL cholesterol concentration but the increase in LDL cholesterol concentration reflects a less atherogenic light LDL subfraction profile that may be favorable"); Harris 1997 at 389 ("The increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however." And "the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD"); Bays III at 248 ("No clinical trial data exist that this rise in LDL-C represents harm or potential "toxicity" to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)"

VLDL particle conversion.[1546] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[1547] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '335 patent are inherent to the compound when administered to a human subject."[1548] Inherency may not supply a missing claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[1549] Obviousness is based on what is *known* in the art at the time of the

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[1546] 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.").

[1547] Bays 2008 I at 400-402.

[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).

invention.[1550] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[1551] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

Defendants argue that the claims of the '335 patent which contain "a limiting clause, such as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively recited and therefore are not elements.[1552] This is incorrect. "There is nothing inherently wrong with defining some part of an invention in functional terms."[1553] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[1554] The claim term "to effect" acts as a positive limitation if the term represents "unexpected and improved effects of administration of the claimed compound."[1555] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the

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[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.").

[1551] *See* discussions below for Grimsgaard, Park, Nozaki Kurabayashi and Hayashi.

[1552] Defendants' Joint Invalidity Contentions at 486.

[1553] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971 )).

[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).

requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

b) Identification of Claim Elements Absent from Each Item of Prior Art

Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent. Where a limitation is absent from any Independent Claim, that limitation is absent from all asserted claims, and that analysis is incorporated by reference into each dependent claim. For any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted claims is not a concession that such limitation is present in the reference. By discussing Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants have appropriately divided the claim language for any purpose.

(1) WO '118

WO '118 discloses a composition containing EPA-E for preventing the occurrence of cardiovascular events in multiple risk patients.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '335 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), WO '118 does not disclose or suggest a subject with the recited very high TG level. WO '118 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty

acid dosage. WO '118 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, WO '118 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, WO '118 does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels who is not on concomitant lipid altering therapy based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(2) WO '900

WO '900 describes methods for obtaining EPA-rich compositions.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '900 disclose or suggest elements of the '335 Claims. The cited portions of WO '900 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of WO '900 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. WO '900 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, WO '900 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, WO '900 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to

Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 5 and 25, this reference does not disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(3) Contacos

Contacos describes a study designed to determine the safety and efficacy of a statin (pravastatin) combined with fish oil either alone or in combination, for the management of patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '335 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of

Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Contacos further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to claim 14, Contacos 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, Contacos 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference

fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

(4) Grimsgaard

Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids, apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG levels.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of the '335 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a subject with the recited very high TG level. Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited administration period. Grimsgaard further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14,

Grimsgaard 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, Grimsgaard does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels who is not on concomitant lipid altering therapy based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(5) Hayashi

Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for 8 weeks. The purity of the composition is not reported. The study was not placebo controlled and was conducted in 28 patients with familial combined hyperlipidemia and a serum tryglceride concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220

mg/dl.

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '335 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a subject with the recited very high TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Hayashi further does not disclose or suggest a method 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, Hayashi 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, Hayashi 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(6) Katayama

Katayama was directed to an investigation of the safety and efficacy of Epadel during long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably, Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '335 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Katayama

further do not disclose or suggest a method 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), Katayama does not disclose or suggest a subject with the recited very high TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Katayama further does not disclose or suggest a method 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, Katayama 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, Katayama 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in

VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(7) Leigh-Firbank

Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '335 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Leigh-Firbank further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to claim 14, Leigh-Firbank 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, Leigh-Firbank 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

(8) Lovaza PDR

The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '335 Claims. The cited portions of the Lovaza

PDR do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Lovaza PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Lovaza PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to claim 14, the Lovaza PDR does not disclose or suggest a method of administering the claimed pharmaceutical composition 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, the Lovaza PDR does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 6, this reference

fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

(9) Maki

Maki administered 1.52g/day DHA supplements to patients with below-average levels of HDL-C. Maki does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '335 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Maki further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Maki further does not disclose or suggest a

method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to claim 14, Maki 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, Maki 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

(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

recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in total cholesterol in the subject with the claimed TG level.

(11) Mori 2000

Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum lipids and lipoproteins, glucose and insulin in humans.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of the '335 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited

portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a subject with the recited very high TG level. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited administration period. Mori 2000 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, Mori 2000 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, Mori 2000 does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels who is not on concomitant lipid altering therapy based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 2, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to

Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(12) Mori 2006

Mori 2006 is a review which reports data from clinical trials which compared the independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '335 Claims. The cited portions of Mori 2006 do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. The cited portions of Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Mori 2006 further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, Mori 2006 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, Mori 2006 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claims 5 and 25, this reference does not disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165

mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '335 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '335 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a subject with the recited very high TG level. Nozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Nozaki further does not disclose or suggest a method 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, Nozaki 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, Nozaki 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(14) Omacor PDR

The Omacor PDR is the Physicians' Desk Reference describing Lovaza.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '335 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest

administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of the Omacor PDR further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction. With respect to claim 14, the Omacor PDR does not disclose or suggest a method of administering the claimed pharmaceutical composition 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, the Omacor PDR does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG and Apolipoprotein B effects in the subject based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 6, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to

effect the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C. With respect to claims 8, 11, 20 and 28, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in non-HDL-C. With respect to claims 9, 12, 22 and 29, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in total cholesterol.

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '335 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Satoh further do not disclose or suggest a method 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), Satoh does not disclose or suggest a subject with the recited very high TG level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Satoh further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, Satoh 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, Satoh does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels who is not on concomitant lipid altering therapy based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(16) Shinozaki

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '335 Claims. The cited portions of Shinozaki do

not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level.

With respect to Claims 1, 14 and 22 of the '335 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a subject with the recited very high TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Shinozaki further does not disclose or suggest a method to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, Shinozaki 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, Shinozaki does not disclose or suggest a method to effect the recited TG and Apolipoprotein B effects in the subject with the recited very high TG levels who is not on concomitant lipid altering therapy based on a comparison to a control subject having the recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 3, 15 and 23, this reference does not disclose or suggest administration to the subject 1 to

4 times per day. With respect to Claims 5 and 25, this reference does not disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '335 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels. The cited portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction 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), Takaku does not disclose or suggest a subject with the recited very high TG level. Takaku also

does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Takaku further does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction in the subject with the claimed TG level. With respect to claim 14, Takaku 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, Takaku 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 recited very high TG levels who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Further, with respect to Claim 2, this reference fails to disclose or suggest the claimed additional lipid outcome based on a comparison to a second subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 5 and 25, this reference does not disclose or suggest the subject having the recited baseline lipid levels. With respect to Claim 17, this reference does not disclose or suggest the subject and the second subject having the recited baseline lipid levels. With respect to Claim 6, this reference fails to disclose or suggest the claimed additional lipid outcomes based on a comparison to a control subject with the recited very high TG levels who has not received the claimed pharmaceutical composition. With respect to Claims 7, 10, 19 and 27, this reference fails to disclose or suggest the recited reduction in VLDL-C in the subject with the claimed TG level. With respect to Claims 8, 11, 20 and 28, this reference fails to disclose or suggest the recited reduction in non-HDL-C in the subject with the claimed TG level. With respect to

Claims 9, 12, 22 and 29, this reference fails to disclose or suggest the recited reduction in total cholesterol in the subject with the claimed TG level.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '335 patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '335 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 14 (and therefore its dependent asserted claims as well): (1) a subject having a fasting baseline triglyceride level of 500 mg/dl to about 2000 mg/dl and *who is not on concomitant statin therapy*; or (2) administering the claimed pharmaceutical composition to the recited subject effective to reduce fasting triglycerides by at least 25% and to reduce fasting Apolipoprotein B, *based on a comparison to a second subject* having a baseline triglyceride level of 500 mg/dl to about 2000 mg/dl who has not received the pharmaceutical composition and is not on concomitant statin therapy.

In addition, Defendants do not contend that the relied upon references disclose the following elements of Claim 22 (and therefore its dependent claims as well): (1) a subject having a fasting baseline triglyceride level of 500 mg/dl to about 2000 mg/dl and *who is not on concomitant lipid altering therapy*; or (2) administering the claimed pharmaceutical composition

to the recited subject wherein upon administering the composition to the subject daily for said period of 12 weeks the subject exhibits a reduction in fasting triglycerides of at least about 25% and a reduction in fasting Apolipoprotein B based on a comparison to a control subject having a baseline triglyceride level of 500 mg/dl to about 2000 mg/dl who has not received the pharmaceutical composition and is not on concomitant lipid altering therapy.

Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '335 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '335 patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claims of the '335 Patent Would Have Been Obvious

(a) Defendants Do Not Demonstrate that a Person of Ordinary Skill in the Art Would Have Had Any Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

(i) The '335 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, Further in View of Nozaki and/or Hayashi and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '335 patent, Defendants present a combination of seven references: "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or

Hayashi, and further in view of Leigh-Firbank and/or Mori 2000."[1556] 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.[1557, 1558] 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.[1559] Defendants' unsupported cobbling

[1556] Defendants' Joint Invalidity Contentions at 479.

[1557] Defendants' bare assertion that the asserted claims are obvious "in view of one or more of Omacor or Lovaza (as described in the references cited above in section V.B.2 in view of, at least, the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2000, Mori 2006, Rambjør, Sanders or Theobald," similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 478-79.

[1558] Defendants' bare assertion that "the motivation or reason to combine or modify 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 477-78.

[1559] *See, e.g.*, *In re Vaidyanathan*, 381 F. App'x 985, 993–94 (Fed. Cir. 2010) ("[W]hile KSR relaxed some of the formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010) (The assertion of a starting point "must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and elements of the prior art compounds.") (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants' contention that claims to (+)-citalopram were "*prima facie* obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988."), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007).

of selective disclosures represents hindsight reconstruction.[1560] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1561] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claims of the '335 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1562]

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[1560] *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").

[1561] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[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.

The analysis of the independent claims of the '335 patent is incorporated into all asserted claims that depend from those claims.

***(a)*** A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '335 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama and/or Matsuzawa Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Both Katayama and Matsuzawa are long term studies directed to an investigation of the safety and efficacy of Epadel in patients with a wide range of baseline TG levels. These studies were not placebo controlled. A person of ordinary skill in the art understood that a placebo may itself cause an effect. Without accounting for the placebo effect, a person of ordinary skill in the art would not and could not attribute any observed effect (and the magnitude of that effect) to that of the drug. Any observed effect could be placebo dependent.[1563] 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

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Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

[1563] *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.)

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 '335 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[1564] This is an incorrect characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C

[1564] Defendants' Joint Invalidity Contentions at 479-80.

levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit[]" is incorrect.[1565] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[1566] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[1567]

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[1565] Defendants' Joint Invalidity Contentions at 479-80.

[1566] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of $PGI_2$ and $PGI_3$ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[1567] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[1568] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[1569] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[1570] Katayama does not disclose *any* LDL-C related data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[1571] In addition to Katayama's lack of disclosure regarding LDL-C,

[1568] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1569] Defendants' Joint Invalidity Contentions at 4679.

[1570] Katayama at 2.

[1571] *Id.* at 16.

Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[1572] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[1573] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[1574] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[1575] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than

[1572] Defendants' Joint Invalidity Contentions at 479.

[1573] Matsuzawa at 7 and 19.

[1574] *Id.* at 23.

[1575] *Id.* at 10.

the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[1576] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[1577] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify

[1576] *Id.* at 11.

[1577] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[1578] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '335 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '335 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person

[1578] *See, e.g.*, Rambjor.

of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[1579] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[1580] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL,

[1579] Nozaki at 256.

[1580] Hayashi at 26, Table I.

to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[1581] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Further, Defendants have failed to offer a purported combination of references as part of their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any motivation to combine Nozaki and Hayashi with the other references of their purported obviousness combinations. Therefore, Defendants should be precluded from relying on these references.

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that

[1581] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[1582] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not* known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either

[1582] Defendants' Joint Invalidity Contentions at 482.

EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA and DHA.[1583] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[1584] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[1585] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-

[1583] Mori 2006 at 96.

[1584] Leigh-Firbank at 440.

[1585] *See, e.g.* Grimsgaard at 654.

C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."[1586] Although teaching away is fact-dependent, "in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[1587]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[1588] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the $HDL_2$-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[1589] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[1590] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA,

[1586] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

[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 (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.").

[1588] Mori 2000 at 1092.

[1589] Mori 2000 at 1088.

[1590] Mori 2000 at 1092.

despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1591] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '335 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or Hayashi, and Further in View of Grimsgaard, Mori 2000 and/or Maki

With respect to the '335 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."[1592] 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

[1591] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[1592] Defendants' Joint Invalidity Contentions at 479-80.

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.[1593] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1594] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1595] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA

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[1593] *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).

[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)

causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claims of the '335 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1596]

The analysis of the independent claims of the '335 patent is incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '335 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported

[1596] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.C.3.c.1.a.i.a.i, incorporated herein by reference, Katayama and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[1597] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[1598] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[1599] Although Grimsgaard states

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[1597] Defendants' Joint Invalidity Contentions at 483.

[1598] Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG levels. (*See* Grimsgaard at Abstract (describing participants as "healthy") and Table 4).

[1599] Grimsgaard at 654.

that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in LDL-C by EPA, as confirmation "that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels."[1600] The results of Grimsgaard, reproduced below, show that EPA and DHA's impact on LDL-C were the same as placebo (corn oil); that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Further, although administration of EPA reduced Apo-B compared to baseline, it was not a statistically significant effect when compared to placebo. Grimsgaard's disclosure highlights the importance of a placebo-controlled study and why results compared only to baseline may be misleading. This type of exaggeration and misinterpretation of the results published in the prior art is seen throughout the Defendants' invalidity contentions.

**TABLE 4**
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

| | DHA ($n$ = 72) | | EPA ($n$ = 75) | | Corn oil ($n$ = 77) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P$[1] | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[3] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[5] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

[1] ANOVA for between-group comparisons of change.
[2] $\bar{x}$ ± SD.
[3–5] One-sample $t$ test of difference between baseline and 7 wk: [3] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$.

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[1601] However, Grimsgaard does not conclude

[1600] Defendants' Joint Invalidity Contentions at 482 n.83.

[1601] Grimsgaard at 657.

that DHA and EPA have differential effects on LDL-C because Table 4 clearly demonstrates that neither DHA nor EPA had a measurable impact on LDL-C. Table 4 demonstrates that EPA and DHA had the same effect on LDL-C. In fact, one of ordinary skill in the art, when reading Grimsgaard, may have been motivated to use purified DHA instead of EPA for the treatment of patients with very-high triglycerides, because net decrease in triglycerides was consistently greater for DHA and DHA caused a statistically significant increase in HDL-C when compared to placebo. Grimsgaard states that "DHA may be responsible for the increase in HDL cholesterol observed with some n-3 fatty acid supplements."[1602] Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard as confirmation "that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[1603] A person of

[1602] Grimsgaard at 654.

[1603]In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make such arguments for the obvious reason that it does not support their argument that EPA was known to have little or no impact on LDL-C levels.

ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the art.[1604] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[1605] based on long-term administration.[1606]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[1607] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[1608]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with

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[1604] Defendants' Joint Invalidity Contentions at 480.

[1605] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[1606] Takaku at ICOSAPENT_DFNDT00006834.

[1607] Takaku at ICOSAPENT_DFNDT00006897.

[1608] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[1609] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in calculating LDL-C levels when triglyceride level is above 400 mg/dL.[1610] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[1611] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other times.[1612] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[1613]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[1614] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary

[1609] Takaku at ICOSAPENT_DFNDT00006884.

[1610] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[1611] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

[1612] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[1613] Takaku at ICOSAPENT_DFNDT00006897.

[1614] Takaku at ICOSAPENT_DFNDT00006897.

skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[1615] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '335 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

[1615] *See, e.g.*, Rambjor.

Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[1616] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[1617] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[1616] Nozaki at 256.

[1617] Hayashi at 26, Table I.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[1618] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Further, Defendants have failed to offer a purported combination of references as part of their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any motivation to combine Nozaki and Hayashi with the other references of their purported obviousness combinations. Therefore, Defendants should be precluded from relying on these references.

(iii) Grimsgaard, Mori 2000 and/or Maki Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[1619] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

[1618] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1619] Defendants' Joint Invalidity Contentions at 482.

known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely on to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Grimsgaard, Mori 2000 and Maki had normal to borderline-high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Grimsgaard, Mori 2000 and/or Maki —as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely on Grimsgaard, Mori 2000 and/or Maki to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[1620] The discussion related to 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 incorporated herein by reference.

Defendants argue that Maki discloses the administration of purified DHA resulted in the desired reduction of TGs, but also significantly increased LDL-C levels.[1621] Maki was designed to assess the impact of 1.52g/day DHA supplements on the serum lipid profile of patients with

[1620] Defendants' Joint Invalidity Contentions at 480.

[1621] Defendants' Joint Invalidity Contentions at 482.

below-average levels of HDL-C levels.[1622] The DHA supplemented group was administered capsules containing 1.52 g/day DHA **and** 0.84 g/day palmitic acid, in addition to other saturated, monounsaturated and polyunsaturated fatty acids. [1623] Therefore, Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[1624] However, one cannot attribute the rise in LDL-C solely to DHA, because the authors admit that "changes in fatty acid intake other than DHA, particularly palmitate, may have also contributed to the elevation in LDL cholesterol."[1625] Further, Maki admits that the "mechanism(s) responsible for the changes in the lipid profile associated with DHA supplementation are not fully understood."[1626] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Defendants mischaracterize the rise in LDL-C associated with the administration of omega-3 fatty acids as being a "negative effect" because they incorrectly focus on only the LDL-C effect and fail to look at the lipid effects as a whole. In fact, Maki does not find the increase in LDL-C to be troublesome; Maki states that "the lack of increase in the total/HDL cholesterol ratio, the decline in the triglyceride/HDL cholesterol ratio and the reduction in the proportion of cholesterol carried by small, dense LDL particles render the changes in LDL cholesterol level

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[1622] Maki at 190.

[1623] Maki at 191.

[1624] Maki at 195.

[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).

[1626] Maki at 197.

less worrisome."[1627] Therefore, when one of ordinary skill in the art reviewed all the lipid effects of the DHA-rich algal triglycerides, they would have understood that the increase is LDL-C was "less worrisome" because of the "potentially favorable effects on triglycerides, the triglyceride/HDL cholesterol ratio and the fraction of LDL cholesterol carried by small, dense particles."[1628]

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1629] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(iii) The '335 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama in View of Satoh and/or in View of Satoh or Shinozaki in Further View of Contacos

With respect to the '335 patent, Defendants present a combination of five references: "the Omacor PDR/Lovaza PDR, in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."[1630] Defendants also present charts purporting to assert that an additional 60 references may be combined in order to render the Claims obvious. Not only do

[1627] Maki at 197.

[1628] Maki at 197.

[1629] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[1630] Defendants' Joint Invalidity Contentions at 480.

Defendants ignore the improbability that a person of ordinary skill would combine 60 separate references, they additionally do not suggest any identify for combining these references. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent reason" to combine must find a basis in the factual record.[1631] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1632] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1633] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the specified fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method

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[1631] *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).

[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)

to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite, that the EPA/DHA composition contained within the reference would cause a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels.

Defendants formulate an obviousness argument that relies on Contacos.[1634] However, Defendants fail to provide any factual or legal basis as to why Contacos discloses a claim element or an "apparent reason" or motivation to combine the elements in the manner claimed,[1635].

Contacos disclosed administration of fish oil, pravastatin, and combination of fish oil and pravastatin, but it does not disclose administration of EPA of the recited composition. Therefore, Contacos fails to provide motivation to administer purified EPA to a very high TG patient population. Contacos also fails to provide motivation to administer purified EPA to a very high TG patient population.

The proposed combinations do not render the independent claims of the '335 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO

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[1634] *Id.*

[1635] *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).

considered Katayama, Satoh, Shinozaki, Contacos, Geppert, Kelley and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1636]

The analysis of the independent claims of the '335 patent is incorporated into all asserted claims that depend from those Claims.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Lovaza with EPA of the Recited Composition

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '335 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.C.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

[1636] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of EPA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation. Satoh reported a statistically significant reduction in LDL-C only when compared to baseline, there was no significant effect when compared to placebo.[1637] Defendants' characterization of Satoh as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[1638] Satoh does not disclose or suggest that the LDL-C results obtained were a clinical benefit, nor would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG below 500 mg/dL and Satoh provides no evidence to the contrary. A person of ordinary skill in the art, however, would have expected that fish oils (and other TG lowering agents) would substantially increase LDL-C in patients with very high TG levels. Satoh fails to provide motivation to administer purified EPA to a very high TG patient population.

Further, Satoh was a small study conducted in only Japanese patients. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be

[1637] Satoh at 145.

[1638] Defendants' Joint Invalidity Contentions at 480.

generalized to other populations.[1639] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) (Lp(a)) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles. Defendants' characterization of Shinozaki as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[1640] Shinozaki says nothing about an LDL-C effect because it measured LDL particle number, not LDL-C. The finding disclosed by Shinozaki was that "long term administration of EPA may lower Lp(a) and serum lipids."[1641] In addition to Shinozaki's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Shinozaki.

Therefore, Katayama, Satoh and/or Shinozaki fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[1642] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki and/or Contacos.

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[1639] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[1640] Defendants' Joint Invalidity Contentions at 480.

[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.

Defendants rely on Geppert and/or Kelley to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels."[1644] Both Geppert and Kelley administer DHA-rich oil that is contaminated with other saturated and polyunsaturated fatty acids. Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[1645] For example, Defendants' own prior art teaches that changes in fatty acid intake other than DHA, particularly palmitate, may contribute to elevations in LDL-C.[1646]

In Geppert, 0.94 g/day of DHA derived from microalgae oil was administered to normolipidaemic vegetarians for 8 weeks. A person of ordinary skill would not have been convinced that DHA increases LDL-C based on Geppert. As Geppert acknowledges, prior studies have shown "[i]nconsistent effects of DHA on LDL cholesterol."[1647] Rather than reading Geppert in isolation, a person of ordinary skill would have read Geppert together with the prior studies cited in Geppert. As such, a person of ordinary skill would have concluded that there was confusion in the art and it was unclear whether DHA increased LDL-C.

A person of ordinary skill would have expected that Geppert's results would be applicable to other components of fish oil such as EPA. Nothing in Geppert suggests that DHA was the only component of fish oil to increase LDL-C. For example, there is no data comparing DHA to fish oil or EPA. In fact, Geppert discusses DHA and fish oil together when trying

[1644] Defendants' Joint Invalidity Contentions at 480.

[1645] *See* Mori 2006 at 96.

[1646] Maki at 197.

[1647] Geppert at 784.

explain the mechanism of LDL-C increase.[1648] A person of ordinary skill would have not expected that EPA and DHA would have different effects on LDL-C based on Geppert.

Defendants contend that Kelley shows that DHA was responsible for the increase in LDL-C.[1649] In Kelley, patients fasting serum TG levels of 150 to 400 mg/dL received 7.5 g/day of DHA oil containing 3 g of DHA for 90 days. Kelley does not show that DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[1650] Further, Kelley teaches that the increase in LDL-C is not harmful when viewed in context with the other lipid effects reported in the study. Kelley states that:

> DHA supplementation may lower the risk of CVD by reducing plasma triacylglycerols; triaclyglycerol:HDL; the number of small, dense LDL particles; and mean diameter of VLDL particles. An increase was observed in fasting LDL cholesterol, but it is unlikely this increase is detrimental because no increase was observed in the overall number of LDL particles; actually, there was an 11% reduction that was statistically not significant. The reason LDL cholesterol increased despite no change in LDL particle number was that the LDL particles were made larger and hence more cholesterol rich by DHA treatment.[1651]

Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Kelley's ultimate conclusion is that "[o]verall, DHA supplementation reduced the concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins" and that "DHA supplementation may improve cardiovascular

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[1648] *Id.*

[1649] Defendants' Joint Invalidity Contentions at 480.

[1650] Kelley at 329.

[1651] Kelley at 329

health."[1652] Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects. Indeed, instead of identifying DHA as composition with negative attributes, a person of ordinary skill would understand that the reference taught towards the use of DHA. In addition, none of the study subjects in Kelley had a TG level above 400 mg/dL and, for the reasons previously discussed, a person of ordinary skill would understand the very high TG patient population to be different in terms of their response to lipid therapy, including administration of DHA. A person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but a person of ordinary skill in the art would expect a substantial increase in LDL-C in patients with very high TG levels.

Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels.

Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1653] As is the case with Kelley, Defendants use hindsight to characterize a reference based on LDL-C levels alone without considering the other lipid effects studied, considered and reported.[1654] The isolated manner in which Defendants select such data points is not the approach that a person of ordinary skill would have taken at the

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[1652] Kelley at 324, 332.

[1653] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1654] Kelley at 324 (providing that the objectives of the study were to determine "the effects of DHA supplementation on the concentrations of apoproteins; large, medium, and small VLDL, LDL, and HDL particles; and the mean diameters of these particles in fasting and postprandial plasma.").

time of the invention. Defendants' approach represents the use of impermissible hindsight bias. A person of ordinary skill would take into consideration the entire disclosure of a reference, including lipid effects other than LDL-C. In pointing only to LDL-C, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. With respect to Kelley, These effects would teach a person of ordinary skill that DHA has a favorable effect in hypertriglyceridemic patients.

Therefore, Geppert and/or Kelley fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1655] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Satoh, Shinozaki, Contacos, Geppert and/or Kelley.

(iv) A Person of Ordinary Skill Would Not Have been Motivated to Find an Omega-3 Fatty Acid "Therapy that Would Reduce TG Levels in Patients with TG Levels ≥500 mg/dL Without Negatively Impacting LDL-C Levels."

Plaintiffs agree that although there was a *need* to find a therapy that would reduce TG levels in patients with very-high TG levels, without negatively impacting LDL-C levels, there was no motivation to find an *omega-3 fatty acid* therapy, or to modify Lovaza/Omacor, to effect a reduction in TG levels without increasing LDL-C levels for very-high TG patients at the time of the invention. A person of ordinary skill in the art understood that the rise in LDL-C caused by omega-3 fatty acids (or fibrates) and Lovaza/Omacor was a consequence of the TG-lowering

[1655] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

mechanism. The therapies that were available at the time of the invention to treat very-high TGs were niacin, fibrates and prescription omega-3 fatty acids (Lovaza/Omacor). However, niacin was associated with a highly undesirable side effects—including "flushing" (or reddening of the face and other areas with a burning sensation) and dyspepsia—that limited their usefulness.[1656] Fibrates were effective at reducing TGs, but they also caused an increase in LDL-C levels in patients with very-high TG levels. To combat the rise of LDL-C, doctors often prescribed fibrates in combination with an LDL-C lowering medication such as a statin.[1657] However, the risk of rhabdomyolysis increased five-fold if fibrates were administered with a statin.[1658] Therefore, physicians were reluctant to recommend, and patients were hesitant embrace, a combination fibrate/statin course of treatment.[1659] Finally, Lovaza/Omacor were also effective at reducing TG levels, but, similar to fibrates, could cause a substantial increase in LDL-C levels for very-high TG patients. However, Lovaza/Omacor could be safely administered with statins in order to mitigate increased LDL-C.

In any event, a person of ordinary skill in the art would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

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[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).

[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");

[1658] *See Id.*; McKenney 2007, at 719 ("[F]ibrates may cause rhabdomyolysis, especially when combined with statins.").

[1659] *See Id.*, ¶ 17

| | 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 Invalidity 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

It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the understanding that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[1664] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[1665] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

In fact, it was well understood that the degree of LDL-C elevation observed with prescription omega-3 therapy, such as Lovaza/Omacor, generally related to pretreatment TG levels; that is, prescription omega-3 therapy, such as Lovaza/Omacor, increased LDL-C levels the most in patients with the highest pretreatment TG levels.[1666] Therefore, a person of ordinary skill in the art would have viewed increased LDL-C levels caused by Lovaza/Omacor as a direct consequence of lowering triglycerides in patients with TG levels ≥500 mg/dL. The rise in LDL-

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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

[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")

[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)

[1666] *See* Bays 2008 Rx Omega-3 p. 402.

C was often offset by concurrent treatment with statins.[1667] The safety and efficacy of using prescription omega-3 in combination with a statin has been well-established.[1668]

Although an increase in LDL-C was generally observed when omega-3 fatty acids were administered to patients with very-high TG levels, the increase in LDL-C was not necessarily a cause for concern because LDL-C is often low in patients with severe hypertriglyceridemia. Therefore, the final LDL-C concentration may still be in the normal range.[1669] Furthermore, it was understood that the overall lipid effect of Lovaza/Omacor was beneficial.[1670]

In two pivotal studies in very-high TG patients, both of which used prospective, randomized, double-blind, placebo-controlled study designs, Lovaza/Omacor increased HDL levels from baseline 13% (p=0.014) and 5.9% (p=0.057).[1671] Correspondingly, prescription omega-3 fatty acids were known to have favorable effects on non-HDL-C levels.[1672] Therefore, "[i]n patients with very-high triglyceride levels, prescription omega-3 fatty acids 4 g/day can substantially reduce triglycerides and VLDL levels and may increase LDL levels, but the net

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[1667] *See* Harris 2008 at 14, McKenney at 722.

[1668] McKenney at 722-23.

[1669] *See* Westphal at 918, Harris 1997 at 389.

[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 chancing LDL structure; lowering serum [cholesteryl ester transfer activity], serum TG and VLDL-C; and increasing serum HDL-C"); Harris 1997 at 389 (stating that "[t]he increase in LDL, which was substantial on a percentage basis, has been a common finding in past studies in [very-high TG] patients. It may not be as problematic as it appears, however," and "the use of omega-3 fatty acids for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the long-term prevention of CHD"); Bays III at 248 ("No clinical trial data exist that this rise in LDL-C represents harm or potential "toxicity" to patients. In fact, most evidence supports that omega-3 fatty acids reduce cardiovascular risk as do fibrates. Importantly, clinical trials mostly support that even with increases in LDL-C, omega-3 fatty acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C)").

[1671] McKenney 2007 at 721 (citing Harris 1997 and Pownall).

[1672] McKenney 2007 at 722 (*see* Fig. 1).

effect is a reduction in non-HDL levels. Modest increases in HDL level are also common in patients treated with prescription omega-3 fatty acids." Prescription omega-3 therapy was also known to alter lipoprotein particle size and composition in a favorable manner by decreasing the number of small, dense LDL particles to larger LDL particles.[1673] Lovaza/Omacor "adversely raise[d] LDL cholesterol concentration but the increase in LDL cholesterol concentration reflect[ed] a less atherogenic light LDL subfraction profile that may be favorable."[1674] Therefore, one of ordinary skill in the art believed that the use of Lovaza/Omacor, and omega-3 fatty acids generally, "for the treatment of severe hypertriglyceridemia may be beneficial not only for the short-term prevention of acute pancreatitis, but also for the longer-term prevention of [coronary heart disease]."[1675]

Therefore, contrary to Defendants' assertion that "a person of ordinary skill in the art at the time of the claimed inventions would have been motivated to find a therapy that would reduce TG levels in patients with TG levels of at least 500 mg/dL without negatively impacting LDL-C levels,"[1676] one of ordinary skill in the art at the time of the invention understood that the rise in LDL-C caused by omega-3 fatty acids was a by-product of reducing TGs in patients with very-high TG levels. A person of ordinary skill in the art would have expected LDL-C to increase in very-high TG patients, and in some instances the rise was not concerning because LDL-C is often low in patients with severe hypertriglyceridemia and therefore final concentration would still be in the normal range. When LDL-C levels increased beyond what was recommended by the ATP-III, prescribers often relied on statins to safely and effectively

[1673] McKenney 2007 at 722 (*citing* Calabresi and Stalenhoef).

[1674] Stalenhoef at 134.

[1675] Harris 1997 at 389.

[1676] Defendants' Joint Invalidity Contentions at 481-82.

reduce LDL-C levels. Furthermore, it was well known that the overall lipid effect of Lovaza/Omacor was beneficial because non-HDL-C levels often increased. Defendants fail to identify any other basis upon which a person of ordinary skill would have been motivated to find a therapy that would reduce TG levels in patients with very-high TG levels without negatively impacting LDL-C levels.

Defendants make the conclusory allegation that "routine optimization" by a person of ordinary skill would yield the claimed invention.[1677] Defendants, however, have offered no explanation to support that allegation and they further fail to establish any of the required criteria of "routine optimization" or the prerequisites to this argument. They also fail to provide any factual detail to support their allegation and they fail to link the allegation to any particular claim or claim element. Defendants mere allegation constitute an improper placeholder to later advance arguments not disclosed in their contentions as required by the Local Rules. In addition, for the reasons discussed herein, a person of ordinary skill would not be motivated to make the combinations alleged by Defendants and, for the same reasons, it would not be routine to combine such references. Where, for example, defendants argue that it would be routine to go from the high TG patient population to the very high TG patient population,[1678] they provide no basis for that conclusory assertion and are incorrect. As discussed, a person of ordinary skill would have understood these patient populations to be distinct with different impacts of lipid therapy on blood-lipid chemistry for each group. Accordingly, a person of ordinary skill would not have considered the dosage modification suggested by defendants to be routine; Defendants' argument to the contrary represents hindsight bias.

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[1677] *See, e.g.*, Defendants' Joint Invalidity Contentions at 477.

[1678] Defendants' Joint Invalidity Contentions at 486-87.

In addition, a person of ordinary skill would have no motivation to combine these references because EPA would have been expected to have same result as the mixture of EPA and DHA used in Lovaza/Omacor.

(v) There Was No Motivation and No Reasonable Expectation of Success in Administering the Claimed EPA Composition to Very High TG Patients to Achieve the Claimed Invention (Including its Apo-B Effects)

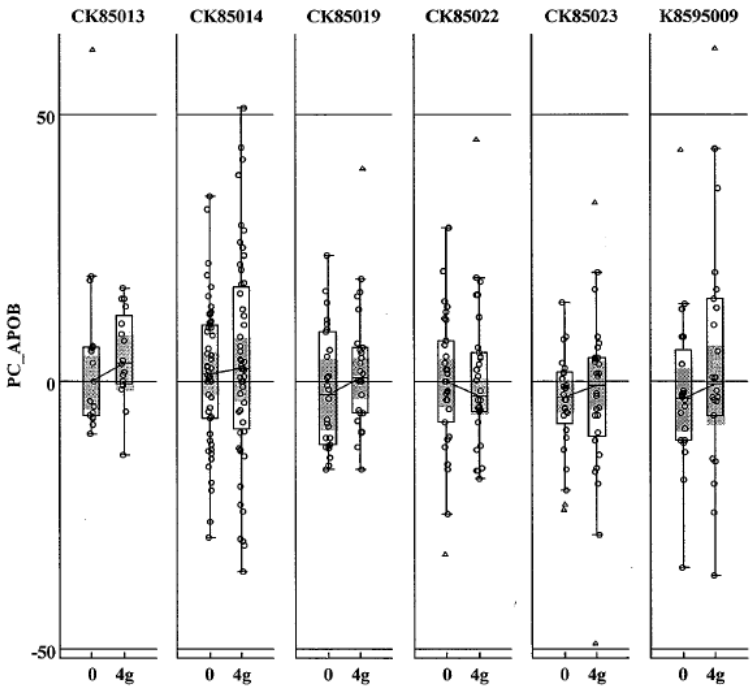
A person of skill in the art would *not* have expected that EPA therapy in very high TG patients would yield a reduction in Apo-B levels (which is a reflection of total atherogenic lipoproteins).[1679] Accordingly, a person of ordinary skill would *not* have been motivated to administer the claimed EPA therapy to the very high TG population and would *not* have had a reasonable expectation of success in achieving the claimed invention (including its Apo-B effects). A person of ordinary skill would have expected the claimed EPA composition would have similar Apo-B effects as the Lovaza clinical trial—the only clinical trial to study the effects of omega-3 fatty acids on Apo-B levels in patients with very high TG levels.[1680] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[1681]

[1679] *see* Section III.

[1680] May 8, 2012 Bays Declaration.

[1681] Lovaza Approval Package at Table 14.

14. Box plot of individual Category I studies -% change of APOB

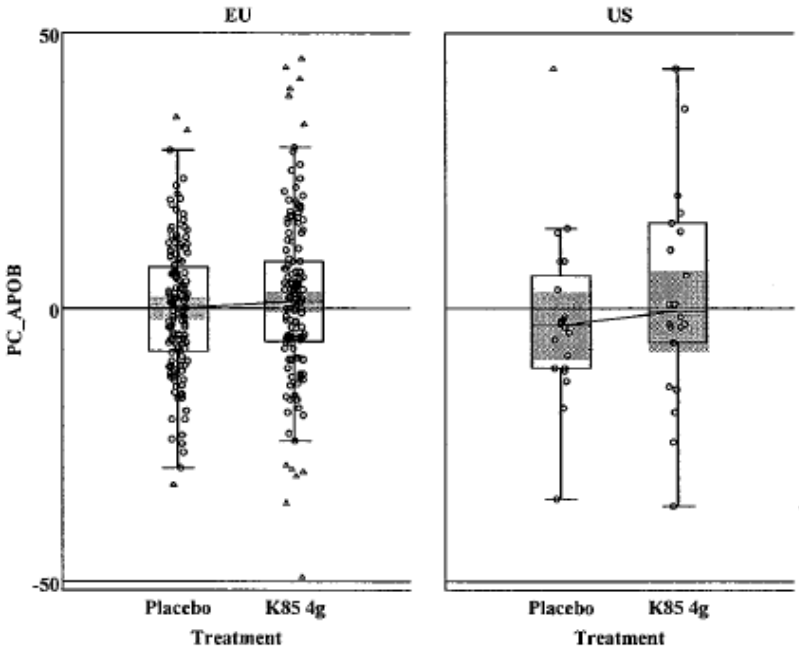



In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[1682] there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza 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.

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[1686] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[1687] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

Accordingly, a person of ordinary skill in the art would not have been motivated to replace EPA with the composition of Lovaza, nor would the person of ordinary skill in the art have been motivated to administer the EPA composition to very high TG patients. For the same reasons, a person of ordinary skill in the art would not have a reasonable expectation of success in achieving the claimed invention.

(b) Defendants Have Not Shown It Would Have Been Obvious to Administer Purified EPA in the Dosing Regimen Recited in the Claims

(i) The '335 Patent is Not Obvious Over WO '118 or WO '900, in Combination With the

[1686] ATP-III at 3170; Bays 2008 I at 395.

[1687] Kwiterovich in Kwiterovich at 4.

Lovaza PDR, and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '335 patent, Defendants present a combination of five references: "WO '118 or WO '900, in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."[1688] Defendants also present charts arguing that an additional 61 references may be combined in order to render the Claims obvious. Not only do Defendants ignore the improbability that a person of ordinary skill would combine 61 separate references, they additionally do not identify any motivation for combining these references. [1689, 1690] 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.[1691] Defendants' unsupported cobbling

[1688] Defendants' Joint Invalidity Contentions at 486-87.

[1689] Defendants' bare assertion that the asserted claims are obvious "in view of one or more of the references cited in Sections III and V.A and B, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobold in combination with the knowledge of a person of ordinary skill in the art in light of the dosing regimen employed with Lovaza/Omacor" similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 486.

[1690] 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 477.

[1691] *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*

of selective disclosures represents hindsight reconstruction.[1692] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1693] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

WO '118 is directed at the composition containing EPA for the purpose of preventing the occurrence of cardiovascular events in multiple risk patients. Further, the invention of WO '118 is directed, "in particular, [to] preventing occurrence of cardiovascular events in hypercholesterolemia patients who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[1694] Contrary to Defendants' assertion that WO '118 discloses "the administration of 4 g of pure EPA with no DHA,"[1695] WO '118 fails to disclose the claimed subject with the specified very high TG levels who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified fatty acid compositions or dosage, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '118 discloses a composition with a wide range of possible EPA

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*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).

[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").

[1693] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1694] WO '118 at 9.

[1695] Defendants' Joint Invalidity Contentions at 487.

content, dosages, and teaches that DHA is a "preferable fatty acid" to include in the disclosed composition.[1696]

WO '118 does not disclose administration of highly-purified ethyl-EPA to the target population of the claimed invention. The asserted claims are directed to persons with severe hypertriglyceridemia (i.e. TG level above 500 mg/dL). WO '118 on the other hand only discloses administration of EPA to persons with triglyceride of at least 150 mg/dL.[1697] WO '118's emphasis on reducing cardiovascular events suggests that its disclosure is directed to patients with borderline-high to high TG levels, since the primary goal for patients with very-high TG is to prevent acute pancreatitis by decreasing TG levels.[1698]

WO '118 also does not distinguish EPA from DHA in its disclosures regarding the effectiveness of the substances for treating hypertriglyceridemia.[1699] WO '118 states that "[a]nother preferable fatty acid . . . is DHA-E," and that "the compositional ratio of EPA-E/DHA-E, content of EPA-E and DHA-E . . . in the total fatty acid, and dosage of (EPA-E + DHA-E) are not particularly limited as long as intended effects of the present invention are attained."[1700] It further states that "the composition is preferably the one having a high purity of EPA-E and DHA-E."[1701] Further, WO '118 does not disclose EPA's effect on LDL-C, VLDL-C, Apo-B, or Lp-PLA2.

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[1696] WO '118 at 22-23.

[1697] WO '118 at 8.

[1698] *See* Section III.

[1699] WO '118 at 11, 13, 16-21 ("the composition containing at least EPA-E and/or DHA-E as its effective component").

[1700] WO '118 at 22-23.

[1701] WO '118 at 23.

WO '900 is directed to a process for producing purified EPA from a culture of micro-organisms. WO '900 fails to disclose the claimed subject with the specified very high TG levels who does not receive concurrent lipid altering therapy, the claimed pharmaceutical composition with the specified dosage or administration period, or the claimed method to effect the specified TG reduction without substantially increasing LDL-C. WO '900 only discloses the method of producing purified EPA for therapeutic use, it does not teach *administration* of pure EPA. WO '900 has no discussion, for example, regarding claimed patient population or method of treatment.

WO '900 does not teach administration of pure EPA to treat hypertriglyceridemia. It lists more than 30 diseases that can be treated with pure EPA, but hypertriglyceridemia is not one of them.[1702] Moreover, WO '900 does not teach the desired effect of EPA other than commenting generally that it "may promote health and ameliorate or even reverse the effects of a range of common diseases."[1703] It has no discussion, for example, on any TG-lowering effect of EPA. Although WO '900 identifies DHA as an "undesired molecule", it does not identify the *specific* undesired effect of DHA or other impurities it is trying to prevent other than commenting generally that "the desired effects of EPA may be limited or reversed" by them.[1704] It has no discussion related to any LDL-C effects caused by DHA.

The proposed combination does not render the independent claims of the '335 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO

[1702] *See, e.g.*, '900 Pub. at 16-17.

[1703] '900 Pub. at 5.

[1704] '900 Pub. at 39.

considered WO '118, WO '900, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1705]

The analysis of the independent claims of the '335 patent is incorporated into all asserted claims that depend from those Claims.

(a) Leigh-Firbank and Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to severely hypertriglyceridemic patients according to Lovaza's known regimen, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Leigh-Firbank or Mori 2000."[1706]

Defendants fail to identify a specific motivation to combine WO '118 or WO '900 with the treatment regimen of Lovaza, as evidenced by the Lovaza PDR. Although Defendants need not point to an explicit statement in the prior art motivating the combination of these references, any assertion of an "apparent reason" to combine must find a basis in the factual record.[1707]

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[1705] *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").

[1706] Defendants' Joint Invalidity Contentions at 487.

[1707] *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

Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1708] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

Contrary to Defendants' assertion, Leigh-Firbank and Mori 2000 do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion regarding Leigh-Firbank and Mori 2000 in Section V.C.3.c.1.a.i.a.iii is incorporated herein by reference. Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention and reflecting no motivation to combine with WO '118 or WO '900. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants

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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).

[1708] *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").

ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1709] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, the Lovaza PDR, Leigh-Firbank and/or Mori.

(ii) The '335 Patent is not Obvious Over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in Combination with the Omacor PDR/Lovaza PDR, and Further in View of Katayama, Matsuzawa and/or Takaku.

With respect to the '335 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."[1710] 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.[1711] Defendants' unsupported cobbling of selective disclosures

[1709] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[1710] Defendants' Joint Invalidity Contentions at 487.

[1711] *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

represents hindsight reconstruction.[1712] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1713] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The discussion related to WO '118 and WO '900 in Section V.C.3.c.1.b.i is incorporated herein by reference. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.C.3.c.1.a.ii.a.iii is incorporated herein by reference. Defendants contend that "Grimsgaard and Mori 2000 also disclose the administration of 4 g per day of highly purified EPA with no DHA." However, neither Grimsgaard nor Mori 2000 discloses the administration of 4g/day EPA to the *very high TG patient population*. Neither Grimsgaard nor Mori 2000 provides motivation to administer 4g/day EPA to the *very high TG patient population*. Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Grimsgaard or Mori 2000.

Defendants argue that it "would have been obvious to a person of ordinary skill in the art to use EPA as described in WO '118, WO '900, Grimsgaard or Mori 2000 in the treatment

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elements of the prior art compounds.") (emphasis in original); *Forest Labs., Inc. v. Ivax Pharm., Inc.*, 438 F. Supp. 2d 479, 492-93 (D. Del. 2006) (rejecting defendants' contention that claims to (+)-citalopram were "*prima facie* obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988."), *aff'd*, 501 F.3d 1263 (Fed. Cir. 2007).

[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)

regimen used for Omacor/Lovaza as described in the Omacor PDR/Lovaza PDR," but their assertions fail to provide a motivation for combining the references.[1714] 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.[1715] Defendants' assertions related to motivation are insufficient,[1716] and accordingly Defendants fail to meet their burden to establish *prima facie* obviousness.

Defendants formulate an obviousness argument that relies on Katayama, Matsuzawa, or Takaku. However, they've failed to provide any factual or legal basis as to why each reference discloses a claim element, an "apparent reason" or motivation to combine the elements in the manner claimed.[1717] Therefore, Defendants should be precluded from relying on this these references.

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[1714] Defendants' Joint Invalidity Contentions at 497.

[1715] *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).

[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).

As discussed above in Section V.C.3.c.1.a.i.a.i, Katayama and Matsuzawa were both only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They fail to provide motivation to administer purified EPA to the very high TG patient population. As discussed above in Section V.C.3.c.1.a.ii.a.i, Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[1718] Further, the study did not include any placebo control, therefore, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[1719]

The proposed combination does not render the independent claims of the '335 patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered WO '118, WO '900, Grimsgaard, Mori 2000, Maki, Katayama, Matsuzawa and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1720]

The analysis of the independent claims of the '335 patent is incorporated into all asserted claims that depend from those Claims.

(a) Grimsgaard, Mori 2000 and/or Maki Do Not Disclose Purported Knowledge that DHA was

[1718] Takaku at ICOSAPENT_DFNDT00006897.

[1719] Yokoyama 2007 at 1097 ("[b]ecause our population was exclusively Japanese, we cannot generalise our results to other populations.")

[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").

Responsible for the Increase in LDL-C

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer pure EPA to hypertriglyceridemic patients according to Omacor/Lovaza's known regimen, Katayama, Matsuzawa or Takaku, particularly in light of the knowledge that DHA is responsible for the increase in LDL-C levels as evidenced by Grimsgaard, Mori 2000 or Maki."[1721]

Contrary to Defendants' assertion, Grimsgaard, Mori 2000 and/or Maki do *not* disclose that DHA is responsible for the increase in LDL-C level. The discussion related to Grimsgaard, Mori 2000 and/or Maki in Section V.C.3.c.1.a.ii.a.iii is incorporated herein by reference. A person of ordinary skill would understand that the results of Grimsgaard demonstrated that EPA and DHA's impact on LDL-C were the same as the effect of the placebo corn oil group; that is, there was no difference between EPA, DHA, or placebo's effect on LDL-C levels. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, the reference does not disclose administration of DHA to the requisite patient population and teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[1722] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Maki demonstrated that when 1.52 g/day DHA **and** 0.84 g/day palmitic acid is

[1721] Defendants' Joint Invalidity Contentions at 488.

[1722] Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

administered to patients with below-average levels of HDL-C levels and borderline-high TG levels, a significant increase in LDL-C is observed.[1723] However, one of ordinary skill in the art knew that saturated fatty acids, such as palmitate, may contributed to the elevation in LDL-C.[1724] Therefore, the results of Maki are inconclusive as to DHA's effect alone on LDL-C levels.

Therefore, Grimsgaard, Mori 2000 and/or Maki fail to substantiate Defendants' assertion that it was known that DHA was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[1725] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine WO '118, WO '900, Grimsgaard, Mori 2000, Maki, the Omacor PDR/the Lovaza PDR, Katayama, Matsuzawa and/or Takaku.

(iii) A Person of Ordinary Skill Would Not Have Been Motivated to Administer Purified EPA in the Treatment Regimen Recited in the Claims

For an invention to be obvious, there must have been an "apparent reason" to make it. Defendants assert that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides."[1726] However, as set forth below, Defendants fail to address why a person of ordinary skill in the art would have

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[1723] Maki at 195.

[1724] 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.").

[1725] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[1726] Defendants' Joint Invalidity Contentions at 488.

been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL.

A person of ordinary skill in the art would have understood that omega 3-fatty acids, including DHA and EPA, and fibrates cause an increase in LDL-C among very high TG patients, as reflected in the prior art. Accordingly, a person of ordinary skill in the art would not have been motivated to look to omega 3-fatty acids in order to obtain a reduction in TGs without increasing LDL-C in very high TG patients:

| | LDL-C Effect | |
|---|---|---|
| | Borderline-High or High TG Patients | Very-High TG Patients |
| Fibrate[1727] | -20% | +45% |
| Lovaza/Omacor[1728] | -6% | +45% |

That Epadel has been approved for decades but not approved for use in the very high TG patient population prior to the invention of the asserted patents is a real-world reflection of the lack of motivation. Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been countless studies conducted which administer Epadel and report the effects observed. Although a few studies administer Epadel to a patient population which included a few patients with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration of Epadel to patients with very-high TG levels, reflecting a lack of motivation.

Defendants further argue that the disclosure in WO '118 would combine with the prior art concerning Lovaza for at least two reasons; first, "products containing DHA were reported to

[1727] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[1728] Chan 2002 I at 2381 (Table 3).

increase LDL-C levels while products containing only EPA did not," and second, "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA."[1729] Both of the "reasons" identified by Defendants are false.

Regarding Defendants' first reason, that "products containing DHA were reported to increase LDL-C levels while products containing only EPA did not," most controlled studies in patients with normal to high baseline TG levels indicated that DHA had little or no effect on LDL-C.[1730] Therefore, a person of ordinary skill would not have concluded that DHA increases LDL-C in patients with normal to high baseline TG levels. Specifically, Leigh-Firbank, Kelley, and Theobald does *not* disclose that "DHA raises LDL-C, an effect associated with heart disease, while EPA does not."[1731] First, Leigh-Firbank cannot comment on the effect of EPA and DHA alone because it did not administer EPA and DHA separately.[1732] A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on lipid parameters. Second, Kelley administered DHA-rich oil that was contaminated with other saturated and polyunsaturated fatty acids.[1733] Therefore, a person of ordinary skill would have known it is unsuitable for evaluating the independent effects of DHA because it is not clear how much of the supplement's effects can be attributed to DHA.[1734] Kelley does not show that

[1729] Defendants' Joint Invalidity Contentions at 488.

[1730] Mori 2006 at 98. Moreover, Mori 2000, the only study which compared EPA versus DHA, and is placebo controlled, found an increase in LDL-C after DHA administration.

[1731] Defendants' Joint Invalidity Contentions at 493.

[1732] The discussion related to Leigh-Firbank in Section V.C.3.c.1.a.i.a.iii is incorporated herein by reference.

[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.

DHA is responsible for the increase in LDL-C. Kelley suggests that increase in LDL-C is a general phenomenon associated with triglyceride-lowering drugs, stating that a similar increase was induced by fibrate therapy.[1735] Kelley specifically teaches that the increase in LDL-C caused by DHA supplementation is unlikely to be "detrimental" because there was not a parallel increase in overall LDL particle number. Rather than concluding that DHA was uniquely responsible for a rise in LDL-C levels, a person of ordinary skill would understand Kelley to disclose that DHA had uniquely beneficial cardioprotective effects.[1736] Finally, Theobald also does not teach that DHA increases LDL-C. In Theobald, 0.7 g/day of DHA was administered for 3 months in patients with normal baseline TG levels. Theobald found that LDL-C increased by 7% when compared to placebo. However, the DHA composition that was administered in Theobald contained significant amounts of other fatty acids, such as myristic acid, palmitic acid, and oleic acid. Therefore, a person of ordinary skill would have known that the DHA administered by Theobald is unsuitable for evaluating the independent effects of DHA because it impossible to determine whether or how much of the supplement's effects can be attributed to DHA.[1737]Contrary to Defendants' assertion that there was "a reported advantage to using EPA vs. DHA in hypertriglyceridemic subjects,"[1738] there was no known advantage to using EPA vs. DHA. In fact, a number of the references Defendants cite in their contentions ultimately conclude that DHA supplementation "may represent a more favorable lipid profile than after

[1735] Kelley at 329.

[1736] 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.")

[1737] *See* Mori 2006 at 96.

[1738] Defendants' Joint Invalidity Contentions at 488.

EPA supplementation."[1739] In addition, a person of ordinary skill would have recognized any impact of DHA reported by the study to be applicable to EPA because they would have understood these substances to function by the same mechanism. Furthermore, as discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels, including healthy patients, as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels.

Regarding Defendants' second reason, that "WO '118 reports a reduction in cardiovascular events in hypertriglyceridemic patients administered highly-purified ethyl-EPA," the cardioprotective effects of omega-3 fatty acids, including both EPA and DHA, have been well documented.[1740] Lovaza/Omacor has been shown to reduce the risk for cardiovascular death plus nonfatal myocardial infarction and nonfatal stroke.[1741] Omega-3 fatty acids have been shown to exert cardioprotective effects in both primary and secondary coronary heart disease prevention trials.[1742] Omega-3 fatty acids were known to reduce TG concentration, have antiarrhythmic effects, decrease platelet aggregation, stabilize plaque, reduce blood pressure and/or reduce heart rate.[1743]

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[1739] Mori 2000 at 1092.

[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.

[1741] *See* Bays, *Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids*, 98 AM. J. CARDIOL 71i (2006) ("Bays 2006").

[1742] Harris et al., *Omega-3 Fatty Acids and Coronary Heart Disease Risk: Clinical and Mechanistic Perspectives*, 197 ATHEROSCLEROSIS 12, 13 (2008) ("Harris 2008").

[1743] Harris 2008 at 13.

Defendants argue that a "person of ordinary skill in the art would have appreciated the fact that highly-purified ethyl-EPA, and not Lovaza, had been demonstrated to reduce cardiovascular events in high-risk hypertriglyceridemic patients, and understood the benefits of replacing the EPA+DHA of Lovaza with the highly purified ethyl-EPA of WO '118."[1744] As discussed above, the cardioprotective effects of omega-3 fatty acids, including both EPA, DHA and Lovaza/Omacor have been well documented.[1745]

In fact, a meta-analysis of twenty-five studies which examined the risk of coronary heart disease endpoints as a function of tissue FA composition found that the evidence suggested that DHA is *more* cardioprotective than EPA.[1746] This study found that "depressed levels of long-chain *n*-3 FA (especially DHA) in tissues is a consistent marker of increased risk for coronary heart disease events."[1747] Further, the study found that DHA levels, with or without EPA, were significantly lower in fatal endpoints.[1748] This study suggests that DHA is preferable to EPA—thus teaching away from the claimed invention.[1749] Defendants rely on hindsight bias to argue that a person of ordinary skill would have been motived to use purified EPA, when both EPA

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[1744] Defendants' Joint Invalidity Contentions at 489.

[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 and CHD risk.") ("Harris 2007").

[1746] Harris 2007 at 8.

[1747] *Id.*

[1748] Harris 2007 at 7, Table 5; *see also* Harris 2007 at 8 ("Low DHA was the most common finding across all studies, suggesting that this FA was perhaps more cardioprotective than EPA as others have suggested.").

[1749] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."); *see also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quoting Gurley); *W.L. Gore & Assocs., Inc. v. Garlock*, Inc., 721 F.2d 1540, 1552 (Fed. Cir. 1983) ("[P]roceed[ing] contrary to the accepted wisdom of the prior art … is strong evidence of nonobviousness.").

*and* DHA were known to have cardioprotective effects, and there were studies suggesting DHA was *more* cardioprotective than EPA.

Defendants argue that the following claim elements were known: the administration of highly-purified EPA-E to reduce TG levels in patients with normal to high TG levels, the administration of purified EPA to patients with TG levels > 500 mg/dL, to administer EPA-E to patients with high and very high TG levels who were not receiving concurrent lipid altering therapy, and the dose of 4g/day and 12-week regimen.[1750] Defendants then argue that the "only question is whether one skilled in the art would have been motivated to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen."[1751]

Defendants' contentions are no more than a recitation that certain claim elements were known in the prior art. Defendants' assertions to the contrary represent hindsight reconstruction.[1752] Notably, Defendants *do not* assert that a person of ordinary skill would have known that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), *would not substantially increase LDL-C.* Further, Defendants point to three Japanese studies,[1753] which included a small minority of patients with baseline TG levels > 500 mg/dL to argue that "a number of prior art references disclosed the administration of purified EPA to patients with TG

[1750] Defendants' Joint Invalidity Contentions at 490.

[1751] Defendants' Joint Invalidity Contentions at 491.

[1752] *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.").

[1753] Nakamura, Matsuzawa, and Takaku.

levels > 500 mg/dL."[1754],[1755] The disclosures of Nakamura (one patient), Matsuzawa (disclosure of three patients with TG between 400 and 1000 mg/dL, with no evidence or support for the assertion that the patients had very high TGs), and Takaku (three patients) reflect that a person of ordinary skill in the art would *not* understand these references to relate to the use of EPA in patients with very high TGs, nor would a person of ordinary skill in the art draw any conclusions regarding these references in terms of the very high TG patient population. In Nakamura, one patient had a baseline TG level > 500 mg/dL.[1756] However, the mean baseline TG for all patients was 2.07 mmol/l (183 mg/dL), indicating that the baseline TG values for the other patients was well below 500 mg/dL.[1757] In Matsuzawa, three patients had TG levels between 400 and 1000 mg/dL and one patient had TG levels > 1,000 mg/dL.[1758] Based on this disclosure, only one patient definitively had a baseline TG level $\geq$ 500 mg/dL. Further, this one patient was excluded when analyzing the lipid impact because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[1759] In Takaku, three patients had baseline TG levels above 500 mg/dL.[1760] However, the mean baseline TG level for all patients was 245 mg/dL.[1761] Indeed, the mean baseline TG level of the patients in all three studies was well below

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[1754] Defendants' Joint Invalidity Contentions at 490.

[1755] Okumura and Hayashi also fail to disclose administration of purified EPA to patients with TG levels > 500 mg/dL. Hayashi states that the baseline TG level was 300 +/- 233 mg/dL. However, the standard error is unusually high and there is no specific disclosure of a single subject with TG levels > 500 mg/dL. Okumuara specifically states that its hypertriglyceridemia patients had baseline TG levels between 150 and 500 mg/dL.

[1756] Nakamura at 23, Table 1.

[1757] Nakamura at 23, Tables 1 and 2.

[1758] *Id.* at 23.

[1759] *Id.* at 10.

[1760] Takaku at ICOSAPENT_DFNDTS00006895.

[1761] Takaku at ICOSAPENT_DFNDTS00006875.

500 mg/dL; therefore, a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Further, in each of these studies, patients with >500 mg/dL were most likely excluded from the LDL-C calculations because the Friedewald's Equation cannot be used for patients with triglyceride levels ≥ 400 mg/dL.[1762] Defendants have failed to identify all of the claimed elements and fail to provide motivation to use the DHA-free, highly-purified EPA-E of the prior art for the treatment of patients with triglyceride levels of at least 500 mg/dL as part of the claimed dosage regimen.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E capsules, for at least 12 weeks . . . in order to achieve the known TG-lowering effects of highly-purified EPA-E."[1763] This argument is flawed. The prior art demonstrates a wide range of administration periods utilized in different clinical studies. For example, EPA was administered for 4 weeks in Park, for 7 weeks in Grimsgaard, for 8 weeks in Hayashi, for 1 year in Takaku, for 2 years in Katayama, and for 5 years in Yokoyama 2007. Given the large number of choices of administration periods disclosed in prior art, Defendants have not shown that a person of ordinary skill would not have been motivated to administer highly-purified EPA-E capsules for 12 weeks and offer no basis for their assertions.

Moreover, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza), for 12 weeks. It was well known that both EPA and DHA reduced blood triglycerides.[1764] In fact, Defendants acknowledge in their Joint Invalidity Contentions that

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[1762] *See* Matsuzawa at ICOSAPENT_DFNDTS00006450.

[1763] Defendants' Joint Invalidity Contentions at 491.

[1764] Mori 2006 at 98.

"DHA and EPA were both known to comparably reduce triglycerides, independently of one another."[1765] Data from some studies even suggested that DHA or fish oil may reduce triglyceride more effectively than EPA.[1766] Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules instead of DHA or a combination of EPA and DHA (such as Lovaza) for 12 weeks.

Defendants argue that a "person of ordinary skill in the art also would have been motivated to administer 4 g/day highly-pure ethyl EPA . . . because of the observed significant reduction in TG that was achieved in six weeks of treatment," citing Mori 2000.[1767] This argument is incorrect. The administration of 4 g/day of highly-pure ethyl EPA to patients with *mild* hypertriglyceridemia for *six* weeks does not provide a person of ordinary skill motivation to administer the same dose to patients with *severe* hypertriglyceridemia for *twelve* weeks. Defendants also, once again, fail to demonstrate that a person of ordinary skill would have chosen to administer 4g/day EPA as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that "because Katayama and Saito 1998 teach that higher doses of highly-purified EPA-E reduce TG level to a greater extent than lower doses . . . a person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E at a dose of 4 g/day rather than a lower dose."[1768] A person of ordinary skill would not have relied on either reference to determine the EPA dosage required to treat severe hypertriglyceridemia,

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[1765] Defendants' Joint Invalidity Contentions at 495.

[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 grater with DHA supplementation than EPA supplementation).

[1767] Defendants' Joint Invalidity Contentions at 491.

[1768] Defendants' Joint Invalidity Contentions at 491.

because these studies were not designed to determine the effect of dose on the degree of TG reduction. Second, Katayama and Saito do not suggest that 4 g/day of EPA, rather than a lower dose or a higher dose, would be the right dosage to treat severe hypertriglyceridemia.

Moreover, as discussed above, it was well known that both EPA and DHA reduced blood triglycerides.[1769] Therefore, a person of ordinary skill would not have been motivated to administer 4 g/day of highly-purified *EPA-E* capsules, as opposed to DHA or a combination of EPA and DHA (such as Lovaza).

Defendants further argue that a "person of ordinary skill in the art would have also been motivated to treat subjects having baseline TG levels of 500 mg/dl to about 1500 mg/dl with highly-purified EPA-E, as suggested by Yokoyama's teaching that TG was reduced to a much greater extent in subjects having higher baseline TG levels . . . and because Katayama and Saito treated subjects having baseline triglyceride levels greater than 500 mg/dl."[1770] This argument is incorrect. It was well known that any TG-reducing therapy will reduce TG to a greater extent in a patient having higher baseline TG levels. Therefore, a person of ordinary skill would not have been motivated to administer highly-purified *EPA-E* capsules as opposed to any other omega-3 fatty acid composition, fibrate, or other TG-lowering therapy, to treat subjects having baseline TG levels above 500mg/dL. Further, a person of ordinary skill would have expected that a greater decrease in TG levels, in the very high TG patient population, would lead to a greater increase in LDL-C levels.

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer highly-purified EPA-E—either on its own or with statin therapy—to effect a

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[1769] *See* Section III.

[1770] Defendants' Joint Invalidity Contentions at 491-92.

reduction in TG levels without affecting LDL-C if treatment was without statin therapy, or to effect a reduction in TG and LDL-C, if treatment was with statin therapy."[1771] Defendants first support this argument by asserting that a person of ordinary skill in the art would have known that EPA could lower TG levels without increasing LDL-C in very high TG patients. That is incorrect. As discussed above, a person of ordinary skill in the art would not have expected EPA to raise LDL-C levels in very high TG patients. Defendants' broadly cite to "Yokoyama 2003, Yokoyama 2007, Mori 2000, Mori 2006, Saito 1998, and the other references discussed in V.B.4. and 5" to support this proposition,[1772] however these references do not disclose or suggest to a person of ordinary skill that EPA could lower TG levels without increasing LDL-C in very high TG patients.[1773]

Defendants next argue again that DHA was known to be responsible for the increase in LDL-C levels in very high TG patients, but as discussed above, *see* Section III, a person of ordinary skill would understand that both EPA and DHA function similarly, and that both would have little to no impact on borderline-high TG patients in terms of LDL-C levels and would increase LDL-C levels in patients with very high TGs.

Defendants argue that a person of ordinary skill in the art "would have known that an increase in LDL-C was an adverse health effect to be avoided."[1774] While an increase in LDL-C was seen as a *possible* adverse health effect, a person of ordinary skill in the art understood that

[1771] Defendants' Joint Invalidity Contentions at 493.

[1772] Defendants' Joint Invalidity Contentions at 493.

[1773] *See* Section IV.

[1774] Defendants' Joint Invalidity Contentions at 495.

the increase in LDL-C seen in the very-high TG patient population with Lovaza, and omega-3 fatty acids generally, was related to increased conversion of VLDL to LDL particles.[1775]

Defendants rely on Kelley and the Lovaza label to argue that "one of ordinary skill in the art would have been motivated, with a reasonable expectation of success, to administer a highly-purified EPA-E dosage form, with little to no DHA, in order to avoid the expected increase in LDL-C with DHA."[1776] However, a person of ordinary skill in the art expected an increase in LDL-C in the very high TG population, with both EPA and DHA. It was well known at the time of the invention that omega-3 fatty acids, including both EPA and DHA, caused significant decrease in the production of VLDL particles and a significant increase in the conversion of VLDL to IDL and LDL, supporting the theory that omega-3 fatty acids worked in part by inhibiting VLDL production and improving the conversion of VLDL particles to LDL.[1777] A person of ordinary skill in the art understood that EPA and DHA had the *same* TG-lowering mechanism and did not differentiate between EPA and DHA when discussing the TG-lowering mechanism of omega-3 fatty acids.[1778] The discussion related to the TG-lowering mechanism of omega-3 fatty acids is discussed above in Section III and incorporated herein by reference.

Accordingly, a person of ordinary skill would not have been motivated to combine WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in with the Omacor PDR/Lovaza PDR, and Katayama, Matsuzawa and/or Takaku. A person of ordinary skill in the art further would not

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[1775] *See* Bays 2008 I at 402; McKenny 2007 at 720 (finding that "[t]hese results illustrate that with prescription omega-3, fewer VLDL particles are secreted into the systemic circulation, and secreted VLDL particles are rapidly converted to LDL particle, thus explaining why LDL levels may increase in patients with very-high triglyceride levels when given prescription omega-3 therapy"); Chan 2003.

[1776] Defendants' Joint Invalidity Contentions at 495.

[1777] 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").

[1778] Bays 2008 I, at 398; Bay *in* Kwiterovich at 247.

have been motivated to combine WO '118 or WO '900, with the Lovaza PDR, or with Leigh-Firbank and/or Mori 2000.

(iv) There Was No Motivation and No Reasonable Expectation of Success in Administering the Claimed EPA Composition to Very High TG Patients to Achieve the Claimed Invention (Including its Apo-B Effects)

A person of skill in the art would *not* have expected that EPA therapy in very high TG patients would yield a reduction in Apo-B levels (which is a reflection of total atherogenic lipoproteins).[1779] Accordingly, a person of ordinary skill would *not* have been motivated to administer the claimed EPA therapy to the very high TG population and would *not* have had a reasonable expectation of success in achieving the claimed invention (including its Apo-B effects).

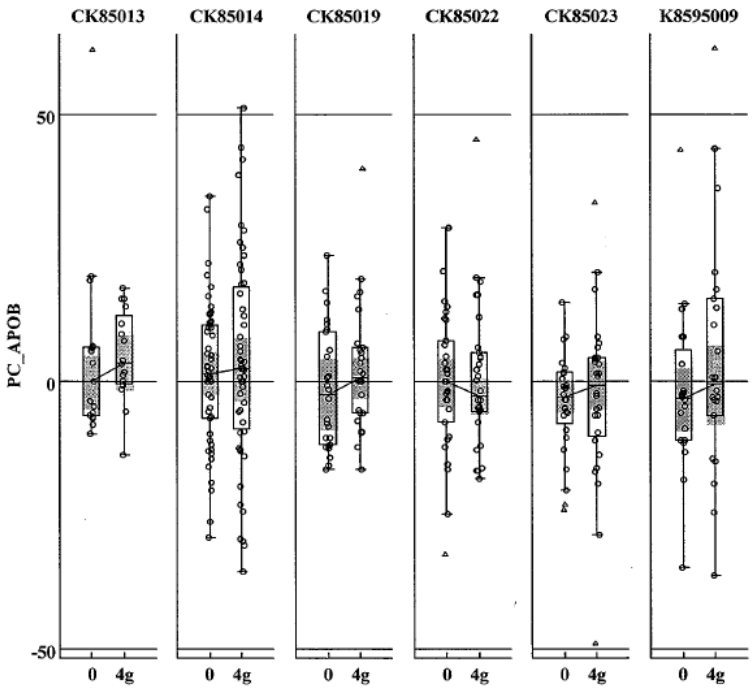
A person of ordinary skill would have expected the claimed EPA composition would have similar Apo-B effects as the Lovaza clinical trial—the only clinical trial to study the effects of omega-3 fatty acids on Apo-B levels in patients with very high TG levels.[1780] The Lovaza clinical trial, which was a large study conducted on patients with very high TG levels, shows no difference between a placebo-control group and the treatment group with respect to Apo-B levels.[1781]

[1779] *See* Section III.

[1780] May 8, 2012 Bays Declaration.

[1781] Lovaza Approval Package at Table 14.

14. Box plot of individual Category I studies -% change of APOB

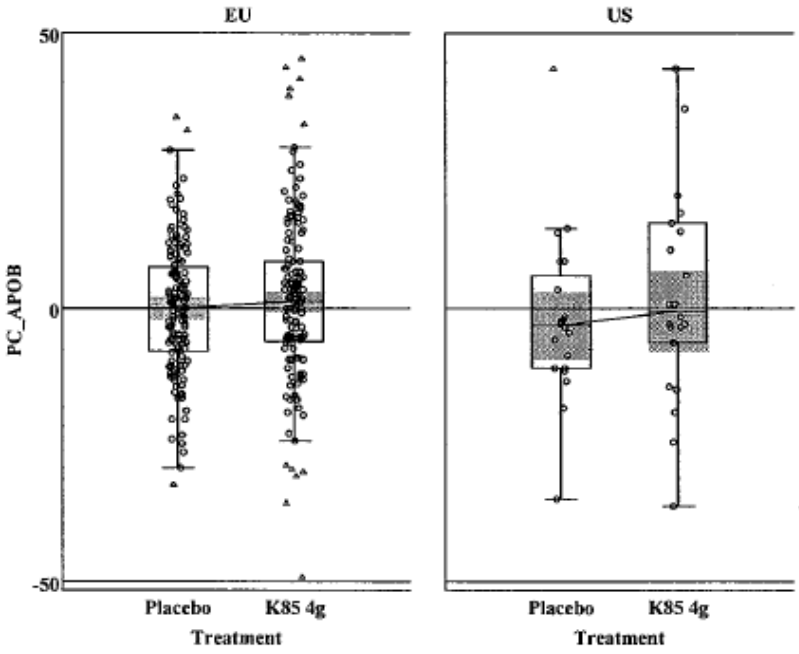



In each of these studies, including K8595009, where subjects had a median baseline TG level of 818 mg/dL,[1782] there was no change in Apo-B between the control and treatment groups. Likewise, pooling the data from the different studies of Lovaza in the EU and US also reflected that treatment with Lovaza 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.

Further, a person of skill in the art would have understood Apo-B to be a surrogate for the number of atherogenic lipoproteins (VLDL, IDL, LDL) present in the body.[1786] The person of skill in the art would also have recognized that, as TG levels in patients with very high TG levels rose, an increasing amount of TGs in those patients were contained within chylomicrons. As discussed above, *see* Section III, the processing of chylomicrons would not yield atherogenic lipoproteins, but instead smaller, denser particles referred to as remnant.[1787] Accordingly, because very high TG patients had increasing levels of TGs stored in chylomicrons and because chylomicron processing would not have been understood to yield changes in Apo-B, a person of skill in the art would have believed that TG-lowering therapies directed to very high TG patients would not significantly impact Apo-B.

Defendants contend that it was "known in the art that Apo-B proteins are components of LDL and VLDL molecules" but do not cite any prior art to support that proposition, instead relying on a declaration by Dr. Bays and ignoring that Apo-B is associated with all atherogenic lipoproteins, including IDL as discussed in Section III, above. Defendants then cite to Kelley for the proposition that it was known that DHA supplementation decreases VLDL diameter and increases the concentrations of small VLDL particles. Subsequently, they argue that because of the increase in small VLDL particles, a person of skill in the art would expect that DHA therapy would increase Apo-B. That is incorrect. As discussed above, *see* Section III, Apo-B is associated with all atherogenic lipoproteins, not simply small VLDL particles. Defendants also assert that DHA was known to increase LDL-C levels, which is incorrect for the reasons discussed above. Further, as discussed above, the Lovaza clinical trials showed that DHA

[1786] ATP-III at 3170; Bays 2008 I at 395.

[1787] Kwiterovich in Kwiterovich at 4.

supplementation in very high TG patients *did not* increase Apo-B levels. A person of skill in the art would have been aware of these data and accordingly would not have expected DHA therapy to increase Apo-B levels in very high TG patients.

Defendants also do not even appear to assert that Kelley renders the asserted claim obvious or identify a combination that includes Kelley. As a result, they necessarily fail explain why there would be a motivation or reasonable expectation of success associated with a combination that would include Kelley. To the extent that Defendants cite Kelley's disclosure to suggest that EPA would have a different impact on lipid parameters than DHA, that argument is incorrect. Kelley does not disclose the use of EPA. Further, Kelley, which was discussed above, *see* Section VI, involved men with an average TG level of 226 mg/dL. A person of skill in the art would not consider the results of Kelly in connection with forming an expectation regarding the impact of EPA therapy on very high TG patients. Defendants fail to make even an assertion to the contrary.

Accordingly, a person of ordinary skill in the art would not have been motivated to administer the EPA composition to very high TG patients. For the same reasons, a person of ordinary skill in the art would not have a reasonable expectation of success in achieving the claimed invention.

(2) Dependent Claims

(a) Defendants Have Not Shown that Claims 2 and 6 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 2 and 6.

Defendants contend, without support, that a person of ordinary skill would reasonably expect that "a pure EPA composition would reduce Apo-B, as it is known to reduce VLDL synthesis." Defendants further contend, without support, that it would have been obvious to a person of ordinary skill to administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also in reducing LDL-C levels. Defendants conclude, without support, that there was a reasonable expectation of success in reducing triglycerides while avoiding an increase in LDL without identifying any combination of references and without explaining how each reference relates to the claimed invention.[1788] These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the

[1788] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

invention of the claim as a whole. Defendants have not met their burden to establish *prima facie* obviousness with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing any support. As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

**(i)** A Person of Ordinary Skill Would Not Have Had a Reasonable Expectation of Success in Replacing the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of successfully obtaining the claimed invention—a method of reducing triglycerides in a subject having very-high triglyceride levels by administering EPA of the recited purity to effect a reduction in triglycerides *with the claimed LDL-C effect*—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.[1789] 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

[1789] 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.

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 administrating 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.

to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides. Indeed, none of clinical studies cited by Defendants are directed to the use of purified EPA in the very-high TG population.

Research into the pharmaceutical uses of EPA started as early as the 1970s. In 1990, Mochida Pharmaceutical, began to market Epadel, a high purity EPA drug. There have been countless studies conducted which administer Epadel and report the effects observed. Although a few studies administer Epadel to a patient population which included a few patients with TG levels > 500 mg/dL, Defendants fail to identify a single reference directed to the administration of Epadel to patients with very-high TG levels. The fact is, a person of ordinary skill did not expect Epadel, which consisted of mostly EPA, to have superior qualities over a drug such as Lovaza/Omacor, which comprised a mixture of EPA and DHA, in patients with very-high triglycerides.

Defendants argue that because Grimsgaard administered purified ethyl EPA to patients with borderline-high/high TG, it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. Defendants base this unsupported conclusion on Grimsgaard, Lovaza/Omacor, the known administration of 2.7 grams of purified EPA to patients with greater than 500 mg/dL TG by Matsuzawa. Defendants' contentions are no more than a demonstration that certain claim elements was known in the prior art and demonstrates impermissible hindsight reconstruction.[1794] As is reflected in Table 4 of Grimsgaard, the study authors found no difference between the DHA, EPA, and control in terms of LDL-C levels. Defendants use hindsight to argue that, despite EPA

[1794] *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.").

and DHA showing the same effect on LDL-C, one would have chosen EPA and expected that administration to very-high TG would have resulted in little or no impact on LDL-C. Notably, none of these references would provide a person of ordinary skill in the art with a reasonable expectation of successfully obtaining the claimed invention even if there were reasons to combine disparate, independent elements found in the prior art, which there were not.

**TABLE 4**
Serum lipids and apolipoproteins at baseline and change after 7 wk of supplementation with docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), or corn oil

| | DHA ($n$ = 72) | | EPA ($n$ = 75) | | Corn oil ($n$ = 77) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P$[1] | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[5] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[3] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

[1] ANOVA for between-group comparisons of change.
[2] $\bar{x}$ ± SD.
[3–5] One-sample $t$ test of difference between baseline and 7 wk: [3] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$.

In addition, Grimsgaard was conducted in patients with normal TG levels, so a person of ordinary skill would have expected no difference between EPA and DHA in terms of LDL-C level change and would have expected no significant increase (or decrease) in LDL-C, as reported by that publication. A person of ordinary skill would further have understood that the data reported by Grimsgaard to be consistent with the understanding that while LDL-C levels are not significantly impacted in normal to high TG patient populations, LDL-C levels would increase significantly in very-high TG patients.

Matsuzawa similarly provides no basis for a reasonable expectation of success in achieving the claimed invention. The subjects of Matsuzawa had a wide range of baseline TG levels and the study was not directed to the very-high TG patient population. Accordingly, just as with Grimsgaard, Matsuzawa would not provide a reasonable expectation of success as a person of ordinary skill would understand patients with very-high TG levels to be different in terms of LDL-C effect than patients with lower TG levels.

To the extent that Defendants' arguments are based on results that are not statistically significant and not reported by Grimsgaard as significant, a person of ordinary skill would not draw conclusions from these statistically insignificant differences. Indeed, the standard deviation for the changes reported is greater than the value of the change itself.

Defendants argue that it would have been obvious to try administering purified ethyl EPA to patients with very-high TG levels with a reasonable expectation of success. However, the Federal Circuit has often rejected the notion that showing something may have been "obvious-to-try" proves that the claimed invention was obvious where the prior art did not suggest what to try.[1795] Rather than there being a limited number of options, the state of the art provided a plethora of compositions and administration protocols associated with multiple kinds of TG-lowering therapies.[1796] There were not a finite number of options for a person of ordinary skill seeking to reduce TG levels without increasing LDL-C among the very-high TG patient population.

Defendants argue that a person of ordinary skill at the time of the invention, based on studies in normal, borderline-high and high TG patients, knew that administration of DHA alone resulted in undesirable increased LDL-C levels while administration of EPA alone had little to no impact on LDL-C levels. However, that statement does not conform with what was known regarding the effect of Epadel and Lovaza/Omacor in normal, borderline-high and high TG patients. Instead as Defendants' own prior art demonstrates, Epadel and Lovaza/Omacor were both known to have little or no effect on LDL-C in patients with borderline-high/high TG levels.

[1795] *See Sanofi*, 748 F.3d at 1360–61.

[1796] *See supra* Section III.

With the lack of any reasonable expectation of success, Defendants argue that their proposed combination amounts to a simple substitution of one known element for another, and that that these changes yield predictable results. Such an argument, however, represents pure and impermissible hindsight bias and further does not consider that reasons for which a person of ordinary skill would not be motivated to combine these references and affirmatives ways in which the art taught away from these combinations.

(ii) A Person of Ordinary Skill Would Not Have Had a Reasonable Expectation of Success in Administering the Purified EPA in the Dosing Regimen Recited in the Claims

Defendants contend that a "person of ordinary skill in the art would have been motivated to administer 4 grams of highly-purified EPA to patients with triglycerides greater than or equal to 500 mg/dL, with a reasonable expectation of success in lowering triglycerides." Defendants also argue that "[a]t least Katayama, Saito 1998, Yokoyama 2007, and Mori 2000 . . . would have given a person of ordinary skill in the art a reasonable expectation of successfully administering 4 g/day of highly-purified EPA-E for at least 12 weeks to lower triglycerides in these subjects relative to baseline or placebo." However, Defendants provide no evidence that a person or ordinary skill would have had a reasonable expectation of success in a method of reducing triglycerides in a subject having very-high triglyceride levels by administering purified EPA to effect a reduction in triglycerides *with the claimed LDL-C effect*. Therefore, Defendants fail to provide a reasonable expectation of success for the claimed invention.

Defendants further argue, that "because it was known that DHA and EPA were comparably efficacious in reducing triglycerides . . . one of ordinary skill in the art would have reasonably expected to see the same hypotriglyceridemic effect from a 4 g/day dose of purified EPA-E as seen with 4 g/day of a combination of both EPA and DHA. Thus, it would have been

obvious to one of ordinary skill in the art to administer a highly-purified EPA-E composition with a reasonable expectation of success that such administration would result in reducing triglycerides while avoiding an increase in LDL." Defendants argument is without any basis. To the contrary, because a person of ordinary skill in the art would have understood DHA and EPA to lower TGs via the same mechanism, the person of ordinary skill in the art would have expected DHA and EPA to have the same impact on LDL-C levels. Defendants provide no explanation and cite to no article to support their argument that the similar effects on TG levels is a basis to differentiate the efficacy of DHA and EPA with respect to LDL-C impact. Based on the hypotriglyceridemic effect alone, a person of ordinary skill would have reasonably expected *both* EPA and DHA, whether administered alone or in combination, would cause an increase in LDL-C when administered to the very high TG patient population.

The prior art taught that DHA and EPA have similar effects on LDL-C levels in patients with very-high TG. A person of ordinary skill would have thus expected EPA, like Lovaza/Omacor, to raise LDL-C levels when administered to the very-high TG patient population. It was well known that TG-lowering agents, specifically fibrates and Lovaza/Omacor, and little or no effect on LDL-C levels for normal to high TG patients, but 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[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 administrating 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).

Accordingly, a person of ordinary skill would not have a reasonable expectation of success in achieving the claimed invention.

(b) Defendants Have Not Shown that Claims 3, 15, and 23 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 3, 15 and 23.

Defendants contend that WO '900, the Lovaza label, Grimsgaard and Mori 2000 teach the additional claim elements of dependent Claims 3, 15 and 15. Defendants contend, without providing any support, that the claim elements are the results of simply optimizing the conditions described in the prior art and within the purview of the skilled physicians. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. None of the cited references discloses administration of the claimed EPA to very high TG patients. Defendants further fail to explain how the cited references can be

combined to teach the administration of the claimed EPA to very high TG patients.[1799] Defendants selectively cite to an unspecified, isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1800] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1801]

Defendants fail to show a motivation or reason to combine or modify the references recited above. Defendants make a conclusory statement that the claimed methods of treatment "would have been obvious to one of ordinary skill in the art," but such a naked assertion does not show why a person of ordinary skill would have been motivated to combine the references to achieve the claimed invention.[1802]

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended

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[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").

[1800] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[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").

[1802] *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356-57 (Fed. Cir. 2007) ("While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ('TSM') test in an obviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

purpose.[1803] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(c) Defendants Have Not Shown that Claims 4, 16, and 24 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 4, 16 and 24.

Defendants contend, without providing meaningful support, that the claim element was well known in the art. These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. Defendants make a conclusory statement that the claimed method of treatment was well known in the art, but such a naked assertion does not show why a person of

[1803] *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.")

ordinary skill would have been motivated to combine the references to achieve the claimed invention.[1804] Further Defendants cite to the "Lovaza product" without identifying the prior art reference to which they refer. Such a reference is inadequate.

Defendants fail to show a reasonable expectation that a person of ordinary skill would have successfully achieved the claimed invention. Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose.[1805] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(d) Defendants Have Not Shown that Claims 5, 17, and 25 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 5, 17 and 25.

Defendants do not identify any combination of references and simply provide a laundry list of references without explaining how each reference relates to the claimed invention. Defendants further contend, without any support, that a person of ordinary skill would have been able to determine the patient population in need of the claimed methods of treatment, would seek

[1804] *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)).

[1805] *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.")

to measure the HDL-C, VLDL-C and cholesterol baselines of a patient, and would seek to treat those patients having very high triglycerides regardless of the baseline values of these lipids.[1806] These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants fail to show a specific combination of references that discloses each element of the claimed invention. Defendants merely list references, without reference to a specific page or section, that purportedly disclose disparate elements without explaining how they can be combined.[1807] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1808] Moreover, by simply identifying prior art references without discussing the specific teachings of each reference, Defendants fail to consider each

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[1806] *Id.*

[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").

[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").

prior art reference as a whole.[1809] Each reference must be evaluated for all that it teaches. Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1810]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that a person of ordinary skill "would indeed seek" to perform the claimed methods of treatment, without providing a reason that would have prompted a person of ordinary skill to combine the elements.[1811] Such a naked assertion does not show why a person of ordinary skill would have been motivated to treat the recited patient population using the claimed methods of treatment.[1812]

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in

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[1809] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("A prior patent must be considered in its entirety, i.e., as a whole, including portions that would lead away from the invention in suit.") (internal citation and quotation marks omitted).

[1810] *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").

[1811] *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)

[1812] *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)).

achieving the claimed invention. In fact, other than simply identifying prior art references that purportedly disclose disparate elements, Defendants do not even discuss whether a person of ordinary skill would have expected that the combination to work for its intended purpose for treating the recited patient population.[1813] As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

(e) Defendants Have Not Shown that Claims 7, 10, 19, and 27 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 7, 10, 19 and 27.

Defendants contend it would have been obvious to use the claimed composition to reduce VLDL-C levels. Defendants further contend that one of ordinary skill would "naturally seek to reduce VLDL-C levels to a therapeutic level." 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,

[1813] *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("[T]he 'predictable result' discussed in KSR refers not only to the expectation that prior art elements are capable of being physically combined, but also that the combination would have worked for its intended purpose.")

Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[1814] As such, Defendants fail to demonstrate that there was no motivation to combine the references to achieve the claimed invention.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants do not even discuss the reasonable expectation of reducing VLDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of reducing VLDL-C levels using the claimed methods.

(f) Defendants Have Not Shown that Claims 8, 11, 20, 28 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims

[1814] *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)).

by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 8, 11, 20 and 28.

Defendants contend that EPA is known to reduce non-HDL-C and VLDL-C levels. Defendants further contend that a person of ordinary skill would have a reasonable expectation that a composition comprising EPA, but not DHA, would lower non-HDL-C levels, citing a laundry list of references without explaining how each reference relates to the claimed invention.[1815] These contentions: 1) do not assert what the prior art discloses to a person of ordinary skill in the art; 2) are irrelevant to an obvious analysis; 3) fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[1816] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1817] Defendants selectively cite to an unspecified isolated

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[1815] *Id.*

[1816] *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").

[1817] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008) ("The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim").

disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1818] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1819]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. In fact, Defendants do not discuss at all whether a person of ordinary skill would have been motivated to combine the elements.[1820] As such, Defendants fail to demonstrate that there was no motivation to combine the references to achieve the claimed invention.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that a person of ordinary skill "would have a reasonable expectation that a composition comprising EPA, but not DHA would lower non-HDL-C levels," without providing a support other than simply identifying prior art references that purportedly disclose disparate elements.[1821] The mere fact

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[1818] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1819] *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").

[1820] *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)).

[1821] *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

that elements are capable of being physically combined does not establish reasonable expectation of success.[1822] What is more, Defendants do not even discuss the reasonable expectation of reducing non-HDL-C levels. As such, Defendants fail to demonstrate reasonable expectation of success of reducing non-HDL-C levels using the claimed methods.

(g) Defendants Have Not Shown that Claims 9, 12, 21, and 29 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claims by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 9, 12, 21 and 29.

Defendants contend, without support, that a person of ordinary skill would naturally seek to reduce total cholesterol level because it represents therapeutic efficacy. Defendants further contend that recited percentage reductions of total cholesterol are obvious because there is no significance regarding the percentage reductions. Defendants conclude, without support, that there was a reasonable expectation of success without identifying any combination of references and without explaining how each reference relates to the claimed invention. 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

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underpinning to support the legal conclusion of obviousness.") (quoting In re Kahn, 441 F.3d 977, 988 (Fed. Cir. 2006)) (internal quotation marks omitted).

[1822] *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.").

success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references and simply provide a laundry list of references that purportedly disclose disparate elements without explaining how they can be combined.[1823] As such, Defendants discuss the claim elements in isolation, and fail to address the claimed invention as a whole.[1824] Defendants selectively cite to an unspecified isolated disclosure within a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[1825] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1826]

Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants make a conclusory statement that "it would have been obvious to the ordinarily skilled artisan to seek to reduce total cholesterol by 5% to 15%," without providing a reason that would have prompted a

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[1823] *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").

[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").

[1825] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1826] *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").

person of ordinary skill to reduce total cholesterol by the recited amount.[1827] Defendants' burden to establish *prima facie* obviousness is not discharged because there is allegedly "no significance" attached to the recited total cholesterol reduction amount.[1828] Defendants have not met the burden with the naked assertion that it would have been obvious to seek the claimed element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing a support other than merely identifying prior art references that purportedly disclose disparate elements.[1829] The mere fact that elements are capable of being physically combined does not establish reasonable expectation of success.[1830]

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[1827] *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)).

[1828] 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).

[1829] *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).

[1830] 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.").

(h) Defendants Have Not Shown that Claims 13 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claim 3.

(i) Defendants Have Not Shown that Claims 18 and 26 of the '335 Patent Would Have Been Obvious

Plaintiffs incorporate by reference the discussion related to the Independent Claims in Section V.C.3. Because Defendants have not shown the obviousness of the Independent Claim by clear and convincing evidence, they also have not adequately proven the obviousness of Claims 18 and 26.

Defendants contend, without support, that a person of ordinary skill would reasonably expect that "a pure EPA composition would effect a reduction in ApoB, as it was known to reduce VLDL synthesis." Defendants further contend, without support, that it would have been obvious to a person of ordinary skill to "administer a composition containing EPA, but containing no DHA, with a reasonable expectation of success in reducing Apo-B levels and thus also in reducing LDL-C levels." Defendants conclude, without support, that there was a reasonable expectation of success in "reducing ApoB levels and thus also in reducing LDL-C levels" without identifying any combination of references and without explaining how each reference relates to the claimed invention.[1831] 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)

[1831] Ando, Calabresi, Contacos, Grimsgaard, Harris, Hayashi, Katayama, Kris_Etherton 2002, Kurabayashi, Leigh-Firbank, Lovaza 2007 Label, Lovaza PDR, Omacor 2004 Label, Omacor PDR, Lovegrove, Matsuzawa, McKenney 2003, McKenney 2007, Mori 2000, Mori 2006, Nakamura, Nestel, Nozaki, Pownall, Sanders, Shinozaki, Takaku, von Schacky, Wojenski, Yokoyama 2003, and/or Yokoyama 2007.

fail to address whether the specific combination of claim elements were all present in the prior art references that would have been combined by a person of ordinary skill in the art to produce the claimed invention with a reasonable expectation of success; and 4) fail to establish *prima facie* obviousness. Defendants do not offer an obvious analysis, but trivialize the claim element to the point of reading the element out of the claim. Although convenient and expedient, Defendants' approach does not conform with the Local Patent Rules of this District, the law of claim construction, or the law of obviousness.

Defendants do not identify any combination of references. Because Defendants do not identify any combination of references, they necessarily fail to offer any evidence that a person of skill in the art would be motivated to combine those references in order to achieve the invention of the claim as a whole. Defendants have not met their burden to establish *prima facie* obviousness with the naked assertion that it would have been obvious to seek the claim element.

Similarly, without the disclosure of a combination of references and a motivation/reason to combine or modify the references, Defendants necessarily fail to offer any evidence that a person of ordinary skill in the art would have had a reasonable expectation of success in achieving the claimed invention. Defendants make a conclusory statement that there was a reasonable expectation of success, without providing any support. As such, Defendants fail to demonstrate reasonable expectation of success of the claimed invention.

**4. The '335 Patent is Not Invalid Under § 112**

a) Defendants Have Not Demonstrated that the Claims of the '335 Patent Are Invalid for Indefiniteness

35 U.S.C. ¶ 112(b) requires that a patentee "particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention."[1832] Patent claims are valid in light of an indefiniteness challenge if they "inform, with reasonable certainty, those skilled in the art about the scope of the invention" in light of the specification and the prosecution history.[1833] The Supreme Court has recognized that "absolute precision is unattainable" in claim language and "the certainty which the law requires in patents is not greater than is reasonable."[1834]

Defendants further allege that the terms "4g per day of a pharmaceutical composition comprising at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate" and "wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined" are indefinite. They contend that, because there is no indication of how much of the pharmaceutical composition is composed of fatty acids, by extension it is indefinite how much of each fatty acid is present in the composition. This is incorrect. A claim can use a ratio to define amounts of components in a product, using terms such as "percent by weight."[1835] In light of the specification and

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[1832] 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.

[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,

prosecution history, a person of ordinary skill would understand with reasonable certainty the range of relative quantities of EPA, DHA and/or other fatty acids in the recited pharmaceutical composition in relation to all fatty acids present.[1836] Therefore, these terms are not indefinite and do not render the claims indefinite.

Defendants allege that a number of terms containing the phrases "about" and "substantially" are indefinite. Defendants do not provide any reason why these terms are indefinite other than that they contain the phrases "about" and "substantially." But, of course, these terms are routinely used in patent claims, and are not *per se* indefinite.[1837] In particular, courts have held repeatedly that claims that contain the words "about" and "substantially" are not indefinite.[1838] Here, a person of ordinary skill would understand with reasonable certainty what is claimed when the claims are read in light of the specification and prosecution history.[1839]

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2011) (construing percent by weight to mean "ratio of the weight of the ingredient in question divided by the total volume of the solution, with this ratio expressed as a percentage").

[1836] *See generally* the '335 patent and its prosecution history.

[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.").

[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).

[1839] *See generally* the '335 patent and its prosecution history.

Therefore, the terms that contain the words "about" and "substantially" are not invalid for being indefinite.

Defendants further allege that the term "who is not on a concomitant lipid altering therapy" is indefinite. Defendants provide no basis for this allegation. In light of the specification and the prosecution history, however, a person of ordinary skill in the art would understand with reasonable certainty the scope of a "concomitant lipid altering therapy."[1840] Moreover, lipid altering therapies are discussed in the patent specification.[1841] Therefore, the phrase "concomitant lipid altering therapy" does not render the claim indefinite.

Defendants further contend that the metes and bounds of the phrases "compared to baseline" and "substantially no increase or a reduction in fasting LDL-C" are unclear. Defendants do not provide the basis for the assertion other than stating that it is unclear and the specification does not clarify its meaning. As discussed above, use of the phrase "substantially" does not render a claim *per se* indefinite. In light of the specification and the prosecution history, a person of ordinary skill in the art would know with reasonable certainty the scope of the terms "compared to baseline" and "substantially no increase or a reduction in fasting LDL-C" and therefore these terms do not render the claims indefinite.[1842]

Defendants also allege that it is impossible to ascertain the metes and bounds of "compared to a second subject [or control subject] having a fasting baseline triglyceride level of 500 mg/dl to about 2000 mg/dl." A person of ordinary skill, however, would understand the metes and bounds of the term in light of the specification and the prosecution history.[1843]

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[1840] *See generally* the '335 patent and its prosecution history.

[1841] See e.g., '335 patent at 12:43-46; 13:66-14:5.

[1842] *See generally* the '335 patent and its prosecution history.

[1843] *See generally* the '335 patent and its prosecution history.

Moreover, the method of comparing a subject to a second subject or control subject, such as a placebo controlled, randomized, double blind study, would have been known to a person of ordinary skill at the time of the invention. Therefore, the term does not render the claims indefinite.

Finally, Defendants contend that the asserted claims improperly mix methods and formulations because Plaintiffs' assertion of contributory infringement apparently suggests that the scope of the claims includes formulations. This is a mistaken interpretation. Indefiniteness analysis is based on what the claim language informs a person of ordinary skill in the art in light of the specification and the prosecution history. Defendants do not identify any actual claim language that mixes methods and formulations. Moreover, contributory infringement may be asserted and proven when a party sells "a material or apparatus for use in *practicing a patented process* . . . knowing the same to be especially made or especially adapted for use in an infringement of such patent."[1844] Plaintiffs assert that Defendants' ANDA products will be used in practicing the claimed methods. Plaintiffs do not assert that the pharmaceutical compound itself directly infringes. Therefore, Defendants' interpretations of Plaintiffs' assertions are mistaken and the '335 patent claims are not indefinite for improperly mixing methods and formulations.

b) Defendants Have Not Demonstrated that the Claims of the '335 Patent Are Invalid for Insufficient Written Description

The first paragraph of 35 U.S.C. § 112 requires that a patent specification "contain a written description of the invention." This requires that the specification "reasonably convey" that the applicant "invented" or "had possession" of the claimed subject matter when the

[1844] 35 U.S.C. § 271(c) (emphasis added).

application was filed.[1845] Support need not be literal[1846]—it may be implicit[1847] or inherent[1848] in the disclosure. In addition, it is unnecessary to include information that is already known or available to persons of ordinary skill.[1849]

Defendants make three arguments regarding the written description requirement. First, Defendants contend that elements reciting the baseline TG levels of the asserted claims lack written description. This is incorrect. The specification of asserted patents literally discloses the claimed invention.[1850] Defendants do not contend that the patient population of the asserted claims is not literally described by the specification. In fact, the specification at the time of filing described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Second, Defendants contend that "a person of skill in the art would not understand that the inventor was in possession of a method incorporating [] specific dosages and quantities." Defendants' assertion is incorrect. The specification of the asserted patents literally discloses the

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[1845] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010).

[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).

[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.

[1848] *In re Gay*, 309 F.2d 769, 771 (C.C.P.A. 1962).

[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.

[1850] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) ("[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."); *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) ("[T]he literal description of a species provides the requisite legal foundation for claiming that species.").

dosages and quantities of the claimed methods.[1851] Moreover, the dosages and quantities of the method appear in the claims, as originally filed. Thus, there is a strong presumption that the claimed invention is adequately described.[1852] Defendants do not and cannot rebut this presumption. For example, the dosage of the composition was originally claimed as "about 1 g to about 4g."[1853] The asserted claims recite "4 g." Defendants do not contend that dosages and quantities of the asserted claims are not literally described by the specification and in the original claims. In fact, the specification and the provisional patent application claims, at the time of filing, described these limitations. Therefore, Defendants have failed to explain whether and how an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention.

Third, Defendants contend that a person of skill in the art would not understand that the inventor was in possession of a method comprising a comparison against a 'baseline' or a second subject. Although this allegation does not appear to implicate written description, the specification describes that the applicants were in possession of the claimed inventions. For example, a person of ordinary skill would have understood that the inventor was in possession of a method comprising administration of a composition with the recited properties, based on a comparison against a baseline or a second subject.

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[1851] *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) ("[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art."); *Snitzer v. Etzel*, 465 F.2d 899, 902 (C.C.P.A. 1972) ("[T]he literal description of a species provides the requisite legal foundation for claiming that species.").

[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 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.

In its 2010 *en banc* decision in *Ariad Pharmaceuticals, Inc. v. Eli Lilly Co.*,[1854] the court elaborated that "possession" means possession as evidenced by disclosure. In this case, the specification of asserted patents literally disclose the claimed invention in the specification and the claims as originally filed. Thus, an examination of the four corners of the specification from the perspective of a person of ordinary skill in the art demonstrates that the inventors of the asserted patents were in possession of the claimed invention.

Defendants conclude by alleging that the specification does not describe anything more than what is obvious, and thus does not provide adequate support for any nonobvious claim. That is incorrect and irrelevant. Nonobviousness does not have to be supported solely by the specification; nonobviousness can be supported by post-filing date evidence for example.[1855] Written description requires only that the specification reasonably conveys that the applicant had possession of the claimed subject matter when the application was filed. Therefore, whether the claims are obvious has no bearing on the adequacy of written description.

c) Defendants Have Not Demonstrated that the Claims of the '335 Patent Are Invalid for Lack of Enablement

The first paragraph of 35 U.S.C. § 112 requires that the specification "enable any person skilled in the art . . . to make and use [the claimed invention]." A claim is not enabled if it would require undue experimentation for a person of ordinary skill to make or use the invention.

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[1854] *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1343-48 (Fed. Cir. 2010).

[1855] *See Sanofi–Aventis Deutschland GmbH v. Glenmark Pharm., Inc.*, 748 F.3d 1354, 1360 (Fed. Cir. 2014) ("Glenmark also argues that later-discovered benefits cannot be considered in an obviousness analysis.... That is incorrect; patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest."); *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (. 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.").

Factors that may be considered include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[1856] The enablement requirement is separate and distinct from the written description requirement,[1857] and as such a claim does not require descriptive support in the disclosure as originally filed for it to be enabled.[1858]

Defendants make two specific arguments regarding the enablement requirement. First, Defendants contend that "[i]t would take undue experimentation to obtain the actual amounts of the composition found in the ultimate claims." This is incorrect. As Defendants admit, the claims disclose amounts of the composition to be administered. Therefore, a person of ordinary skill would be able to determine the amounts of the components in the pharmaceutical composition without any experimentation, much less undue experimentation.

Second, Defendants contend that it would take undue experimentation to obtain the claimed required results listed in the full scope of the patent claims, including the claimed lipid effects. This is incorrect. The asserted claims require no experimentation to practice the claimed method and certainly not undue experimentation. Administration of a recited amount of a recited composition, for a recited duration, to a specific, recited patient population produces the recited results. No additional experimentation is required, and Defendants do not explain their allegation that undue experimentation would be required. Defendants also do not contend that following the claimed method (each recited element) does not produce the recited results. The

[1856] *See, e.g.*, *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[1857] *Vas-. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)

[1858] MPEP § 2164.

clinical studies included in the VASCEPA® label and submitted to the USPTO clearly demonstrate that administration of EPA of the recited composition, when administered to patients with very high TG levels for at least 12 weeks, as specified, produces the recited results.[1859] Therefore, the claims are not invalid for lack of enablement.

Defendants conclude by alleging that the specification does not enable anything more than what is obvious over the prior art or was known to a person of skill in the art. First, Defendants do not cite any case or present a legal theory to support this assertion. As such, they do not allow Plaintiffs to adequately respond to the assertion. Therefore, Defendants should be precluded in the future from raising any new legal theory to support this assertion. Moreover, while the '335 patent's specification enables a person of ordinary skill to obtain the claimed limitations without undue experiment, the claimed limitations would not have been obvious to a person of ordinary skill, as discussed in Section V.C.3. Furthermore, Plaintiffs have initiated human clinical trials and submitted the trial results to the USPTO to substantiate the utility of its claimed methods.[1860, 1861] Therefore, a person of ordinary skill would have concluded that the claims possessed credible therapeutic utility, and the full scope of the claims was enabled.

[1859] *See* VASCEPA Prescribing Information at Table 2.

[1860] *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995) (Post-filing evidence "can be used to substantiate any doubts as to the asserted utility."); MPEP § 2107.03 ("[A]s a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.").

[1861] *See* May 16, 2011 Bays Declaration at Appendix B.

D. **The '399 Patent**

**1. The '399 Patent Claims Eligible Subject Matter Under § 101**

Defendants' allegation that the asserted claims of the '399 patent relate to ineligible subject matter under Section 101 is without merit. Defendants do not establish a *prima facie* case under Section 101 or provide a legal or factual basis to support their allegations.

As an initial matter, Defendants' disclosure is also insufficient under the Nevada Local Patent Rules as the grounds for any allegation of invalidity under Section 101 must be provided.[1862] The bare assertion of invalidity under Section 101 without providing the grounds for such an allegation and examining the elements of the asserted claims of the '399 patent does not meet this requirement and thwarts the purpose of the Rules.[1863]

The inquiry under Section 101 involves a two-step test: first, a court must determine whether the claim at issue is directed to a patent-ineligible concept: a law of nature, physical phenomenon, or abstract idea.[1864] Second, even if the claim is directed to one of these concepts, it still may be patent eligible and the court must determine what else is part of the claim.[1865]

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[1862] *See* Nevada Local Patent Rule 1.8(e) ("[E]ach party opposing a claim of patent infringement, shall serve on all other partiesNon-Infringement, Invalidity, and Unenforceability Contentions that must include . . . A detailed statement of any grounds of invalidity based on 35 U.S.C. § 101.").

[1863] Nor does the preceding paragraph, which provides only a purported summary of the claims of the '399 patent, or subsequent paragraph, which makes what appears to be an argument entirely unrelated to Section 101, provide the grounds for Defendants' allegation of invalidity under 35 U.S.C. § 101. *See, e.g.*, *Silver State Intellectual Techs., Inc. v. Garmin Int'l, Inc.*, 32 F. Supp. 3d 1155, 1161–62 (D. Nev. 2014) ("The District of Nevada's Local Patent Rules, like the local patent rules for the Northern District of California, are designed to require the parties to provide early notice of their infringement and invalidity contentions, and to proceed with diligence in amending those contentions when new information comes to light in the course of discovery") (internal quotation marks omitted).

[1864] *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.").

[1865] *Id*. (quoting *Mayo*, 132 S. Ct. at 1294) ("If so, we then ask, '[w]hat else is there in the claims before us?'").

The sole Section 101 case identified by Defendants, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), is inapplicable to the asserted claims of the '399 patent. In *Mayo*, the claims were directed to "well-understood, routine, [and] conventional" steps, and the only novel element related to administering the proper dosage based on a natural law observation.[1866] However, the claims merely recited this natural law without reciting any novel application of it.[1867] The Court found that providing protection to such claims would result in pre-empting "a broad range of potential uses" and excluding others from using "the basic tools of scientific and technical work."[1868] A method of treatment claim, specifying the subjects, dosage levels, composition, and time course does not raise the concerns of *Mayo* and instead is akin to the typical claims which *Mayo* acknowledges are entitled to patent protection.[1869]

Defendants suggest that the recited EPA composition of each asserted claim is a naturally occurring substance. It is not. Even references contained within Defendants' own contentions make clear that EPA of the requisite purity and characteristics is not found in nature.[1870] As expressed by the patents cited in Defendants' contentions and well-established precedent, for decades it has been accepted that compositions isolated from nature or purified beyond their

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[1866] *Mayo*, 132 S. Ct. at 1294.

[1867] *Id.* at 1301.

[1868] *Id.*

[1869] *Id.* at 1302 (contrasting the patent-ineligible claims of that case to "a typical patent on a new drug or a new way of using an existing drug); *see also Diamond v. Diehr*, 450 U.S. 175, 177 , 191-193 (1981) (upholding patentability for "a process for curing synthetic rubber which includes in several of its steps the use of a mathematical formula and a programmed digital computer" under Section 101); *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016) (finding claims patent eligible because by holding otherwise, a host of other patent eligible claims, such as method of treatment claims, would also be necessarily ineligible).

[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).

natural state are patent-eligible.[1871] Moreover, Defendants' assertions are immaterial to a Section 101 defense because method of treatment claims like the ones asserted in this case are patent eligible even if they are directed to administration of a naturally occurring substance.[1872]

To the extent Defendants are arguing that a law of nature both underlies the claims and renders them ineligible, that argument is unsupported and incorrect. Defendants allege that "the claimed effects are the natural result of ingesting a naturally-occurring substance."[1873] Since the composition that is the subject of the claims is not naturally occurring, Defendants appear to suggest that all method of treatment claims involve a law of nature. That is not what *Mayo* states or even suggests, and indeed the Federal Circuit has refused to adopt Defendants' overbroad characterization of laws of nature.[1874] To say that the claims of the '399 patent claim a law of nature is to suggest that all patents claim such laws and engage in an infinitely regressive mode of analysis that the Supreme Court did not adopt in which "all inventions can be reduced to underlying principles of nature" that would "make all inventions unpatentable."[1875] Indeed, even

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[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).

[1872] *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1048-49 (Fed. Cir. 2016).

[1873] *See* Defendants' Joint Invalidity Contentions at 522.

[1874] See *CellzDirect*, 827 F.3d at 1048-49 ("The [asserted] claims are like thousands of others that recite processes to achieve a desired outcome . . . . That one way of describing the process is to describe the natural ability of the subject matter to *undergo* the process does not make the claim 'directed to' that natural ability. If that were so, we would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells' inability to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin).").

[1875] *See Mayo*, 132 S. Ct. at 1034 (quoting *Diamond v. Diehr*, 450 U.S. 175, 188 (1981)).

those concerned about the implications of *Mayo* on future patents were focused on diagnostic claims not treatment claims of the type that *Mayo* stated were typical and patentable.[1876]

Even if there is some underlying law of nature in the asserted claims, the subject matter of the '399 patent remains eligible for protection under Section 101. As articulated by *Mayo* and *Diehr*, patents claiming a law of nature, such as a mathematical equation, are entitled to protection where claims "did not 'seek to pre-empt the use of [the] equation,' but sought 'only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process.'"[1877] As discussed above, the asserted claims of the '399 patent contain a novel, unconventional, and specific method of treatment comprising a particularized application of a nonnaturally occurring substance and does not preempt the use of a law of nature.[1878]

Defendants also argue that any argument by Amarin in response to Defendants' § 112 arguments are further evidence of invalidity under § 101. This argument is without merit. The claims are enabled and written description is satisfied for the reasons discussed below. In addition, as discussed above, the asserted claims are not merely a naturally-occurring phenomena, and thus satisfy the requirements of § 101.

[1876] *See Mayo*, 132 S. Ct. at 1034 ("Prometheus, supported by several *amici*, argues that a principle of law denying patent coverage here will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research.").

[1877] *See Mayo*, 132 S. Ct. at 1299 (quoting *Diehr*, 450 U.S. at 187).

[1878] *See, e.g.*, *Tannas Electronics v. Luxell Technologies, Inc*., 2012 WL 3800822, at *4 (C.D. Cal. July 24, 2012) (rejecting a challenge to the patentability of a claim under Section 101 where the alleged natural phenomenon was "just one step in the whole process" claimed by the invention).

### 2. The Asserted Claims of the '399 Patent Are Not Anticipated by WO '118

To anticipate, a single prior art reference must sufficiently describe a claimed invention so that the public is in "possession" of that invention.[1879] Therefore, to anticipate, a reference must set forth every element of the claim, either expressly or inherently, in as complete detail as is contained in the claim.[1880] The claim elements must also be "arranged" in the prior art reference, just as they are in the claim,[1881] rather than as "multiple, distinct teachings that the artisan might somehow combine to achieve the claimed invention."[1882] In addition, public "possession" requires that the prior art enable a person of ordinary skill to make and use the invention without undue experimentation.[1883] Factors that may be included in this analysis include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.[1884] This inquiry is objective, and thus evidence of undue 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).

[1880] *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).

[1881] *Bond*, 910 F.2d at 833; *Akzo*, 808 F.2d at 1479.

[1882] *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).

[1883] *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).

[1884] *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

[1885] *Plant Genetic Sys., N.V. v. DeKalb Genetics Corp*., 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); *Liquid Dynamics Corp. v. Vaughan Co., Inc*., 449 F.3d 1209, 1224–25 (Fed. Cir. 2006); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1336 (Fed. Cir. 2003); *Gould v. Quigg*, 822 F.2d 1074, 1078 (Fed. Cir. 1987).

Defendants assert that Claims 1-9 of the '399 Patent are anticipated by the WO '118 reference.[1886]

A element-by-element analysis, identifying each element of each asserted claim that is absent from WO '118, is provided below. The contentions below are incorporated by reference into Exhibit D, and vice-versa. WO '118 does not anticipate the claims of the '399 patent because it does not describe, properly arrange, or enable the '399 patent claims.

a) WO '118 Does Not Teach Every Element of the Claims of the '399 Patent

(1) WO '118 Does Not Describe the Claimed Lipid Effects

It is well established that, for a prior art reference to anticipate, "every element of the claimed invention must be identically shown in a single reference."[1887] Moreover, the elements of the claimed invention must have "strict identity" with the elements of the reference; "minimal and obvious" differences are sufficient to prevent anticipation.[1888] Here, WO '118 entirely fails to disclose the following elements of Claim 1 of the '399 Patent: *to effect a reduction in triglycerides without substantially increasing LDL-C compared to a second group of subjects having a median fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who have not received the pharmaceutical composition and a concurrent lipid altering therapy.* Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any basis for concluding that WO '118 teaches this element.[1889] Indeed, Defendants

[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.

[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).

[1888] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

[1889] Defendants' Invalidity Contentions at 202-204.

could not set forth any basis for concluding that WO '118 teaches this element because WO '118 does not.

Instead, Defendants argue that these elements express the intended result of a method that is positively recited, and therefore is inherently anticipated. However, for the reasons set forth below, WO '118 fails to disclose each element of the independent claim of the '399 Patent, either expressly or inherently. Therefore, WO '118 cannot anticipate the claimed method. Defendants also argue that these elements represent inherent, natural properties of EPA, and are entitled to no patentable weight. This conclusion is incorrect and inconsistent with the law of anticipation and claim construction. Further, while Defendants argue that the inherent properties are exemplified in the prior art, they fail to identify even a single prior art reference that makes such a disclosure. Defendants cannot point to a single, specific prior art reference because the claimed pharmaceutical composition has never been administered in the manner claimed to the claimed patient population. Also, these elements are positively recited in the body of the claim and therefore cannot be construed as a non-limiting preamble and must be given patentable weight.

Further, Defendants entirely fail to prove that inherently discloses the claimed lipid effects. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[1890] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[1891] "It is not sufficient if a material element or limitation is 'merely probably or

[1890] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[1891] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

possibly present' in the prior art."[1892] WO '118 fails to provide any data related to the lipid effects of the disclosed invention on patients described in the publication. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the elements of the independent claim every time it is administered.

Defendants fail to demonstrate that administration of the claimed EPA compositions "*necessarily*" yields the claimed lipid effects. For example, one study cited by Defendants suggests that EPA administration may increase LDL-C.[1893] Rambjor is a clinical study which administered EPA, DHA, fish oil or placebo to human subjects. Rambjor showed that both EPA and fish oil caused a significant increase in LDL-C. On the other hand, DHA effected only a non-significant increase in LDL-C. As reflected by the disclosure of Rambjor, EPA does *not* decrease TG without increasing LDL-C *every time it is administered*.

Therefore, WO '118 cannot anticipate the independent claim of the '399 patent. Because the dependent claims include all of the claim elements of the independent claim, WO' 118 cannot anticipate any of the dependent claims as well.

(2) WO '118 Does Not Disclose Methods of Treating The Claimed Patient Population

In addition, WO '118 fails to disclose or suggest the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population. Defendants attempt to eliminate these important elements by arguing that the preamble is non-limiting. A preamble is the introductory clause of a patent claim and includes everything from the beginning of the claim until a transitional phrase, such as "comprising." Defendants improperly attempt to truncate the preamble.

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[1892] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[1893] *See, e.g.*, Rambjor.

A claim preamble has patentable weight if, "when read in the context of the entire claim, [it] recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim."[1894] Additionally, the preamble constitutes a claim element when the claim depends on it for antecedent basis because "it indicates reliance on both the preamble and claim body to define the claimed limitation."[1895]

The preamble of the asserted claims is limiting for several reasons. The term "subject" in the preamble of the independent claim defines and provides antecedent basis for the "subject" recited in the body of the claims. When reading the claim, one must rely on both the preamble and the claim body to define the claimed invention.

If the preamble states "a fundamental characteristic of the claimed invention," then it "is properly construed as a limitation of the claim itself."[1896] The recitation of a "method of reducing triglycerides" in the preamble provides antecedent basis for the effect of reducing triglycerides in the body of the claim and emphasizes the intentional purpose for which the method must be performed - to reduce triglycerides.

It is clear that "the claim drafter chose to use both the preamble and the body of the claim to define the subject matter of the claimed invention."[1897] Thus, the entire preamble in the independent claim of the '399 must contain patentable weight.

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[1894] *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999) (citation omitted).

[1895] *Catalina Marketing Int'l v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002) (citation omitted).

[1896] *Poly-Am. L.P. v. GSE Lining Tech., Inc.*, 383 F.3d 1303, 1309 (Fed. Cor. 2004); *see also e.g., Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1375 (Fed. Cir. 2008) (concluding the preamble phrases "portable computer" and "portable computer microprocessing system" limit the claims because they "clearly recite a necessary and defining aspect of the invention, specifically its portability," and because the specification and prosecution history "emphasize this feature of the invention").

[1897] *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 953 (Fed. Cir. 2006).

WO ‘118 fails to disclose the patentable elements of the preamble of the asserted claims. WO ‘118 does not describe or suggest that the claimed pharmaceutical composition be administered in the manner claimed to the claimed patient population.

First, WO ‘118 fails to expressly disclose “a method of reducing triglycerides.” In fact, the invention disclosed by WO ‘118 relates to a composition for **preventing occurrence of cardiovascular events**, as evidenced by the title which reads “Composition for Preventing the Occurrence of Cardiovascular Event in Multiple Risk Patient.” The prevention of the occurrence of cardiovascular events is defined in WO ‘118 as “all cases of primary prevention, and exemplary cases include prevention of cardiovascular death, fatal myocardial infarction, sudden cardiac death, nonfatal myocardial infarction, cardiovascular angioplasty, new occurrence of rest angina and exercise-induced angina, and destabilization of the angina.”[1898] The invention of WO ‘118 is intended to be administered to any person in need of prevention of the occurrence of cardiovascular events, who are typically hypercholesterolemia patients.[1899] WO ‘118 does not expressly describe its invention as a “method of reducing triglycerides,” therefore it cannot anticipate the independent claim.

Second, WO ‘118 fails to disclose the subject as described in the claims. Defendants fail to prove that these elements of the claimed invention have “strict identity” with the elements of the reference.[1900] WO ‘118 fails to anticipate this claim element because the broad disclosure fails to anticipate the narrow claimed range, and the specific patient population defined in the claims is an essential part of the claimed invention.

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[1898] WO ‘118 at 12.

[1899] *Id.*

[1900] *Trintech Industries, Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002).

There is no evidence in that subject as described in the claims were ever treated. In fact, WO '118 fails to disclose baseline lipid levels of a single subject. Defendants rely on the definition of "hypertriglyceridemia" in WO '118 to argue that WO '118 discloses treatment of the subject as described in the claims. It does not. Defendants' argument rests on the definition in WO '118 of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL." WO '118's definition is not tied to a specific subject and there are no working examples, data or other reference in WO '118 indicating that any subject with fasting TG levels of at least 500 mg/dL received an EPA composition as claimed in the asserted patents, or any EPA at all. In addition, Defendants rely on a reference to "Omacor" in WO '118 (at 32) as evidence that a "person of ordinary skill in the art would have understood that the term 'hypertriglyceridemia' when used in the WO '118 includes patients with triglyceride levels of 500 mg/dL to about 1500 mg/dL." The cited section states that "soft capsules" are preferable and then merely provides examples of commercially available "soft capsules," such as Omacor. The passage does not define "hypertriglyceridemia" as used in WO '118 as referring to patients with triglyceride levels over 500 mg/dL. Nor does it suggest that the claimed EPA should be used in the over 500 mg/dL TG patient population. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot inherently anticipate as a matter of law."[1901] Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets the claim elements of the independent claim every time it is administered.

Further, the broad range disclosed by WO '118 is insufficient to anticipate the ranges claimed by the '399 patent. In *Atofina*, the prior art disclosed a temperature range of 100 to 500 degrees and a preferred range of 150 to 350 degrees; the patent at issue claimed a range between

[1901] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

330 and 450 degrees. The court found that the broader prior art range could not anticipate the claimed temperature range, "[g]iven the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this element of the claim."[1902] A prior art's teaching of a broad genus does not necessarily disclose every species within that genus. The court explained the slightly overlapping range between the preferred range and claimed range "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1903] and therefore failed to anticipate the claimed range. Likewise, WO '118's broad disclosure of hypertriglyceridemia as a "fasting serum triglyceride levels of at least 150 mg/dL" does not anticipate the subject as described in the claims because it fails to described the claimed TG range with sufficient specificity.

The court in *Atofina* ruled on an additional question of anticipation that also involved a range of numbers. A prior art reference had disclosed a range of 0.001 to 1.0 percent, as compared to the patent's claimed range of 0.1 to 5.0 percent.[1904] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1905] Similarly, although there may be overlap between the definition of hypertriglyceridemia taught by WO '118 and the TG range recited by the claims of the asserted patents, WO '118 does not specifically discuss, highlight or otherwise suggest treating patients with TG values above 500

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[1902] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006).

[1903] *Atofina*, 441 F.3d at 1000.

[1904] *Id.*

[1905] *Id.*

mg/dL. In fact, WO '118 is directed to compositions and methods for preventing occurrence of cardiovascular events, suggesting that the treatment was envisioned for patients with TG levels below 500 mg/dL (the patient population the ATP III identifies the prevention of atherogenic events as the primary clinical objective),[1906] WO '118, therefore, does not expressly disclose the specific patient population that is an essential element of the claims of the asserted patents. Therefore, WO '118 cannot anticipate the claims of the asserted patents.

The treatment of a patient with elevated TG levels varies depending on their serum triglyceride levels. Identification of the patient population with very high TG levels (at least 500 mg/dL) is central to the claimed invention. In the 2000s, physicians treating lipid disorders, including hypertriglyceridemia, relied on the ATP-III for authoritative guidance on the treatment of lipid disorders.[1907] The ATP-III divided hypertriglyceridemia patients into three classes based on the levels of TG in their blood—borderline-high (150-199 mg/dL), high (200-499 mg/dL), and very-high TGs (≥ 500 mg/dL)—and recommended substantially different treatment strategies for patients depending on classification.[1908] For the borderline-high and high TG groups (150-499 mg/dL), the primary goal was to reduce risk of coronary heart disease.[1909] Accordingly, in these populations, physicians focused on lowering LDL-C.[1910] In this patient population, lowering of TG and non-HDL-C levels were considered secondary treatment goals. In contrast, the primary goal for very-high TG patients (≥ 500 mg/dL) was to reduce the risk of pancreatitis—a potentially life threatening condition expected to be precipitated by elevated

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[1906] *See* Section III.

[1907] *Id.*

[1908] ATP III at 3335; *See also* Section III.

[1909] *Id.*

[1910] *Id.*

TGs— by lowering TG levels. In very high TG patients, lowering LDL-C is a secondary treatment goal.[1911] Therefore, as evidenced by the ATP-III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint.

Therefore, WO '118's definition of "hypertriglyceridemia" as "fasting serum triglyceride levels of at least 150 mg/dL" fails to anticipate the claimed subject with very high TG levels. In fact, as described above, WO '118 is not directed toward patients with the claimed TG levels at all. WO 118's disclosure is clearly directed towards preventing the occurrence of cardiovascular risk, which is the primary aim for treatment of patients with high triglycerides (200-499 mg/dL). Thus, WO '118's disclosure is *not* directed towards patients with very high triglyceride levels (where the primary goal is to prevent acute pancreatitis and damage to the pancreas by decreasing triglycerides), as required by the independent claims of the asserted patents, and therefore cannot anticipate the independent claim of the '399 Patent.

Third, WO '118 fails to disclose the claim element of "a second group of subjects . . . who have not received the pharmaceutical composition and a concurrent lipid altering therapy." Defendants' only basis for concluding that WO '118 teaches this element is that WO '118 "discloses and claims the administration of EPA-E without the administration in combination with statins."[1912] This sentence appears to be incomplete, as it is unclear what Defendants mean by "without the administration in combination with statins." This single statement, without

[1911] *Id.*

[1912] Defendants' Invalidity Contentions at 46.

citation to a single page in WO '118, fails to demonstrate that WO '118 teaches this element. In fact, WO '118 methods comprise statins, i.e. HMG-CoA RI.[1913]

WO '118 states that its disclosed composition is "effective in preventing occurrence of cardiovascular events in hypercholesterolemia patients, and **in particular**, in preventing occurrence of cardiovascular events in hypercholesterolemia patient who have been treated with HMG-CoA RI but still suffer from the risk of the cardiovascular events."[1914] WO '118 goes on to state that the "effect of the composition of the present invention will be synergistically improved by combined use with the HMG-CoA RI, and such use of the composition of the present invention with the HMG-CoA RI has clinical utility since the effect of preventing the cardiovascular event occurrence is expected to be improved."[1915] Administering the composition of WO '118 with HMG-CoA RI is disclosed as preferred because of the synergistic effect HMG-CoA RI has on the disclosed compound. Further, WO '118 teaches that the disclosed composition may be used with a long list of other drugs, including lipid altering drugs such as antilipotropic drugs and fibrate drugs.[1916] Thus, WO '118 does not disclose administration of the claimed EPA compositions to a subject that has very high TG levels and also "a second group of subjects . . . who have not received the pharmaceutical composition and a concurrent lipid altering therapy," and cannot anticipate the independent claim of the '399 patent. In fact, the example of the methods of WO '118 expressly teaches a statin/EPA co-therapy. Because the dependent claims depend from the independent claim, they include the elements of the

[1913] HMG-CoA RI stands for HMG-CoA reductase inhibitor; also known as statins, these inhibitors are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase.

[1914] WO '118 at 9 (emphasis added).

[1915] *Id.* at 10.

[1916] *Id.* at 24-25.

independent claim. Thus, WO '118 cannot anticipate any of the dependent claims of the '399 patent.

(3) WO '118 Does Not Describe the Claimed Pharmaceutical Composition or its Specific Administration

WO '118 further does not anticipate the claims of the '399 patent because it does not disclose "administering orally to the subject." As WO '118 fails to disclose the subject as claimed, it cannot anticipate oral administration to the claimed "subject."

WO '118 additionally cannot anticipate the claims of the '399 patent because it does not disclose administering the pharmaceutical composition at a dose of about 4g per day. Defendants argue that this element is disclosed by WO '118's teaching that the daily dose is "typically 0.3 to 6 g/day." Defendants fail to provide the entire disclosure of WO '118, which states that the daily dose is "typically 0.3 to 6 g/day, preferably 0.9 to 3.6 g/day, and still more preferably 1.8 to 2.7 g/day. Another preferable daily dose is 0.3 to 2.7 g/day, and 0.3 to 1.8 g.day. Another preferable fatty acid included is DHA-E." WO '118 teaches that the dosage is not particularly limited as long as the intended effect, preventing the occurrence of cardiovascular events, is attained. However, Defendants fail to provide any evidence that a dose that is effective to prevent the occurrence of cardiovascular event, is also a dose that would be effective to reduce triglycerides in the claimed patient population. Furthermore, there are no working examples, data or other reference in WO '118 indicating that any subject (much less one with fasting TG levels of at least 500 mg/dL) received an EPA composition as claimed in the asserted patents or any EPA at all, much less at the claimed dose of 4 grams/day.

As discussed above, in *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic

range of 330 to 450 °C,"[1917] and therefore failed to anticipate the claimed range. The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[1918] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this limitation of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1919] Similarly, although there may be some overlap between the daily dose disclosed by WO '118 and the dose claimed by the '399 patent, WO '118 does not specifically highlight the overlapping area and, moreover, the range claimed by the '399 patent does not fall within WO '118's preferred range. Defendants conveniently omit the preferred range and mischaracterize the teaching of WO '118. Notably, the example indicates that up to 900 mg of the EPA composition could be used three times per day (2.7 g). Thus, WO '118 does not expressly disclose the 4 g per day dose claimed by the '399 patent and cannot anticipate the independent claim of the '399 Patent.

WO '118 further does not anticipate the claims of the '399 patent because it does not disclose the claimed EPA pharmaceutical composition. Defendants once again cite only a portion of the disclosure and exclude sections that show the breadth of WO '118's teachings. WO '118's full disclosure recites that "the EPA-E used is preferably the one having a high purity, for example, the one having the proportion of the EPA-E in the total fatty acid and derivatives thereof of preferably 40% by weight or higher, more preferably 90% by weight or higher, and still more preferably 96.5% by weight or higher."[1920] Therefore, WO '118 discloses

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[1917] *Atofina*, 441 F.3d at 1000.

[1918] *Id.*

[1919] *Id.*

[1920] WO '118 at 22.

EPA-E with "high purity" is a composition which contains EPA-E of 40% by weight, of total fatty acid and derivatives, or higher. This non-specific disclosure is not a species of the claimed generic range for the EPA composition in the claimed pharmaceutical composition.

The Federal Circuit has explained that "a preferred . . . range . . . that slightly overlaps the . . . range claimed in the" patent is insufficient for anticipation.[1921] In *Atofina*, the prior art disclosed a preferred temperature range of 150 to 350 degrees, and the patent at issue claimed a range between 330 and 450 degrees. The court explained that this slight overlap "is not disclosed as . . . a species of the claimed generic range of 330 to 450 °C,"[1922] and therefore failed to anticipate the claimed range.[1923] The court in *Atofina* also found that a prior art disclosure of a range of 0.001 to 1.0 percent failed to anticipate the patent's claimed range of 0.1 to 5.0 percent.[1924] The court explained that "although there is a slight overlap, no reasonable fact finder could determine that this overlap describes the entire claimed range with sufficient specificity to anticipate this element of the claim. The ranges are different, not the same. . . . Thus, there is no anticipation."[1925]

Similarly, although there may be some overlap between the E-EPA content disclosed by WO '118 and the ranges claimed by the '399 patent, WO '118 does not specifically highlight the overlapping area. The high content of E-EPA in the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '399 patent. Therefore, WO '118's broad

[1921] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 1000 (Fed. Cir. 2006).

[1922] *Atofina*, 441 F.3d at 1000.

[1923] *Atofina*, 441 F.3d at 1000.

[1924] *Id.*

[1925] *Id.*

disclosure of the E-EPA content in its invention does not describe the claimed range with sufficient specificity and cannot anticipate the independent claim of the '399 patent.

WO '118 is additionally insufficient for anticipation because it does not expressly disclose the recited DHA content of the claimed pharmaceutical composition. In fact, WO '118 makes no distinction between EPA and DHA, stating that "[a]nother preferable fatty acid is DHA-E."[1926] The disclosure goes on to state that the composition of the invention is preferably one having high purity of EPA-E and DHA-E. The recited DHA content of the claimed pharmaceutical composition is a critical factor of the invention disclosed in the '399 patent.

The disclosure of WO '118 treats DHA and EPA interchangeably. The disclosed concentrations of EPA and DHA may range from 0 to 100% and every concentration in between. There is no express teaching or guidance directing the person of ordinary skill in the art to the claimed EPA compositions, Therefore, WO '118's broad disclosure, which indicates no difference between the use of EPA or DHA in its invention, cannot anticipate the independent claim of the '399 patent.

Defendants contend that Plaintiffs are estopped from arguing there is any material difference between "not more than about 4% DHA" and "substantially no DHA." Defendants provide no legal basis for their argument of estoppel. Defendants appear to suggest that testing data obtained by Plaintiffs constitutes the basis for their assertion of estoppel. That argument is without merit. Plaintiffs' clinical data cannot form the basis for an estoppel argument and Defendants have cited no authority to support their position suggesting the contrary. The language of "not more than about 4% DHA" and "substantially no DHA" are different phrases and are not co-extensive. Accordingly, plaintiffs are not estopped.

[1926] WO '118 at 22.

In the same paragraph containing their allegation of estoppel, Defendants also quote from Amarin's 2011 10-K. It is unclear whether these quotations are associated with their unexplained estoppel arguments. To the extent that they are, Plaintiffs disagree that these statements form the basis for any theory of estoppel. To the extent that Defendants quote Amarin's post-invention 10-K to make any invalidity argument, that is also unavailing. The quoted statements do not identify any recited claim element, including the specific pharmaceutical composition, the recited patient population, administration in the manner claimed, and recited lipid effects. Nor can these elements of the asserted claims be inferred from the quoted statements.

(4) WO '118 Does Not Describe the Dependent Claims

Defendants fail to address any of the claim elements of the dependent claims. Defendants appear to concede that WO '118 does not expressly teach these elements, as they fail to set forth any meaningful basis for concluding that WO '118 teaches these elements. Defendants further argue that "aspects of the claims relating to effects that are to be achieved by practicing the claimed method represent inherent, natural properties of EPA, and are entitled to no patentable weight." To the extent the recited claim elements relate to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method, Defendants' contentions that the claim limitations are inherent properties of EPA are unavailing. While Defendants assert that the inherent properties are exemplified in WO '118, they fail to identify any basis, explanation, or even supporting argument for that assertion. Defendants have not met the burden to establish anticipation with the naked assertion that the effects are inherent, natural properties of EPA.

Further, Defendants entirely fail to prove that inherently discloses the recited claim limitations. A prior art reference that "only 'probably' or 'possibly' meets the claims cannot

inherently anticipate as a matter of law."[1927] "[A]nticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation."[1928] "It is not sufficient if a material element or limitation is 'merely probably or possibly present' in the prior art."[1929] Defendants fail to show that WO '118 "*necessarily"* meets the recited claim elements relating to the administration step, the dosage form or characteristics of the treated subject and the specific effect produced by the claimed method *every time*. WO '118 fails to provide any data related to the TG, LDL-C, VLDL-C, non-HDL-C, Lp-PLA2, total cholesterol, Apo-B, or any other lipid effect of the disclosed invention on patients described in the publication. Further, WO '118 is a translated Japanese disclosure that makes no reference to, let alone a disclosure of, a Western diet. Therefore, Defendants fail to prove by clear and convincing evidence that the composition disclosed by WO '118 meets any dependent claim elements.

### 3. The Claims of the '399 Patent Would Not Have Been Obvious In Light of the Asserted References

Defendants identify 77 separate references that it asserts somehow render the claims of the '399 Patent obvious.[1930] Defendants fail to demonstrate by clear and convincing evidence that any of these references, alone or in combination, would render obvious any claims of the '399 Patent. Defendants' arguments rely on hindsight by impermissibly using the blueprint of

[1927] *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999).

[1928] *Transclean Corp. v. Bridgewood Servs., Inc.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002) (emphasis in original).

[1929] *In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1378 (Fed. Cir. 2007).

[1930] Defendants' Joint Invalidity Contentions at 13-25.

the '399 Patent itself to guide its combination of references.[1931] Defendants chart a laundry list of 77 separate references, without explanation. Defendants' disclosures do not comply with Local Patent Rule 1-8(d) and fail to put Plaintiffs on notice of how these references allegedly establish that the asserted claims are allegedly *prima facie* obviousness. Consequently, Plaintiffs cannot respond to undisclosed combinations and arguments.[1932]

Despite the general, non-limiting nature of Defendants' Joint Invalidity Contentions, Plaintiffs have discerned and will specifically respond to the following alleged prior art combinations:

- 1) ". . .the asserted claims of the '399 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi, and further in view of Leigh-Firbank and/or Mori 2000."

- 2) ". . .the asserted claims of the '399 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering purified EPA as evidenced by Katayama, Matsuzawa and/or Takaku, further in view of Nozaki and/or Hayashi, and further in view of Grimsgaard, Mori 2000 and/or Maki."

- 3) ". . .the asserted claims of the '399 patent would have been obvious over the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama in view of Satoh and/or in view of Satoh or Shinozaki in further view of Contacos."

- 4) ". . . the asserted claims of the '399 patent would have been obvious over WO '118 or WO '900 in combination with treatment regimen of Lovaza as evidenced by the Lovaza PDR, and further in view of Leigh-Firbank and/or Mori 2000."

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[1931] *In re Suong-Hyu Hyon*, 679 F.3d 1363, 1371 (Fed. Cir. 2012) ("It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is obvious." (citing *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992))).

[1932] This includes Defendants' improper attempt to incorporate by reference any alleged prior art or argument, including Defendants' attempt to incorporate by reference "the reasons set forth in the opposition proceedings for EP 2 395 991 B1" in the European Patent Office. Such wholesale incorporation by reference does not satisfy the Defendants' obligations or burden of proof and is contrary to the Nevada Local Patent Rules, which require that each prior art be identified specifically. *See* Local Pat. R. 1-8. Plaintiffs reserve the right to strike any attempt to rely on undisclosed or insufficiently disclosed references or argument.

- 5) ". . . the asserted claims of the '399 patent would have been obvious over WO '118, WO '900, Grimsgaard, Mori 2000 and/or Maki in combination with treatment regimen of Omacor/Lovaza as evidenced by the Omacor PDR/Lovaza PDR, and further in view of Katayama, Matsuzawa and/or Takaku."

A patent claim is invalid "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."[1933] 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.[1934]

In evaluating obviousness, each prior art reference must be evaluated for all that it teaches, including the portions that would lead away from the claimed invention.[1935] Indeed, any teaching in the art that points away from the claimed invention must be considered.[1936] A reference teaches away if a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.[1937] For instance, a reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant.[1938]

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[1933] 35 U.S.C. § 103(a).

[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).

[1935] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1936] *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1359-60 (Fed. Cir. 1999)

[1937] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)

[1938] *Id*.

In order to find obviousness based on a combination of references, there must be some rationale for combining the references in the way claimed that is separate and apart from the hindsight provided by the patented invention itself.[1939] The law prohibits an obviousness challenge based on a hindsight reconstruction of the claimed invention from isolated prior art references. It is improper for "the claims [to be] used as a frame, and individual, naked parts of separate prior art references [to be] employed as a mosaic to recreate a facsimile of the claimed invention."[1940] "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made."[1941]

"The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."[1942] "[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."[1943] "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known."[1944]

Accordingly, it is improper to pick and choose isolated elements from the prior art and combine them so as to yield the invention[1945] or to modify a prior art reference in a way that

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[1939] *Immogenetics, N.V. v. Abbott Labs*, 512 F.3d 1363, 1373–74 (Fed. Cir. 2008)

[1940] *See W.L. Gore & Assoc., Inc. v. Garlock, Inc*., 721 F.2d 1540, 1552 (Fed. Cir. 1983)

[1941] *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996)

[1942] *Sanofi Syntheolabo v. Apotex, Inc*., 550 F.3d 1075, 1086 (Fed .Cir. 2008)

[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))

[1944] *KSR*, 550 U.S. at 418-419.

[1945] *Abbott Labs v. Sandoz, Inc.*, 544 F.3d 1341, 1348 (Fed. Cir. 2008)

"would destroy the fundamental characteristics of that reference."[1946] Moreover, a combination is not obvious where "it would be impossible to apply these teachings [of the secondary reference] to the [primary reference] without entirely changing the basic mechanism and procedure thereof,"[1947] or where the proposed combination requires "material and radical modification in order to conform to [the patentee's] claims" or a "total reconstruction" of the prior art device.[1948] Furthermore, it is improper "to modify the secondary reference before it is employed to modify the primary reference" in assessing obviousness.[1949]

Further, a party asserting obviousness in view of a combination of prior art disclosures must show that a person of ordinary skill in the relevant field had an "apparent reason" to combine the elements in the manner claimed[1950] and "a reasonable expectation of success."[1951]

For chemical compounds, there must have been a reason both to select the prior art compound "most promising to modify" and to make the necessary changes to arrive at the claimed compound.[1952] This protects against the use of hindsight to pick through the prior art

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[1946] *Apple, Inc. v. Samsung Elec. Co., Ltd.*, 678 F.3d 1314, 1331 (Fed. Cir. 2012)

[1947] *In re Irmscher*, 262 F.2d 85, 87 (CCPA 1958)

[1948] *Id*. at 88.

[1949] *In re Hummer*, 241 F.2d 742, 745 (CCPA 1957)

[1950] *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).

[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 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).

[1952] *Daiichi Sankyo Co. v. Matrix Labs. Ltd*., 619 F.3d 1346, 1354 (Fed. Cir. 2010); *Takeda*, 492 F.3d at 1355, 1359–60; P&G, 566 F.3d at 994–95; *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd*., 533 F.3d 1533, 1358 (Fed. Cir. 2008); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 471 F.3d 1369, 1378–80 (Fed. Cir. 2006).

based solely on structural similarity to the claimed compound.[1953] Any assertion of an "apparent reason" must find a basis in the factual record.[1954]

The "reasonable expectation of success" for a chemical compound must be of all of a claimed compound's relevant properties,[1955] including those discovered after the patent was filed or even issued.[1956] "The basic principle behind this rule is straight-forward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious."[1957] Any assertion of a "reasonable expectation of success" must find a basis in the factual record.[1958]

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[1953] *Daiichi Sankyo*, 619 F.3d at 1354; *Pfizer*, 2010 WL 339042, at *14. *Accord In re Vaidyanathan*, 381. 985, 994 (Fed. Cir. 2010) (nonprecedential); *Processing Corp. v. Am. Maize-Products Co*., 840 F.2d 902, 907 (Fed. Cir. 1988); *Power-One*, 599 F.3d at 1351–52; *Crown Ops. Int'l., Ltd. v. Solutia, Inc*., 289 F.3d 1367, 1376 (Fed. Cir. 2002).

[1954] *See, e.g., Vaidyanathan*, 381. at 993–94 ("[W]hile KSR relaxed some of the formalism of earlier decisions requiring a 'teaching, suggestion, or motivation' to combine prior art references, it did not remove the need to anchor the analysis in explanation of how a person of ordinary skill would select and apply the teachings of the references. . . . Obviousness is determined as a matter of foresight, not hindsight."); *Daiichi Sankyo*, 619 F.3d at 1354 (The assertion of a starting point "must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention." This turns on the known "properties and elements of the prior art compounds."); *Forest Labs.*, 438 F.Supp.2d at 492–93 (rejecting defendants' contention that claims to (+)-citalopram were "prima facie obvious in light of . . . claims [to] racemic citalopram" despite its use to "treat the same condition," and concluding that defendants "have not demonstrated by clear and convincing evidence that one skilled in the art would have been motivated to resolve citalopram in June 1988").

[1955] *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000) ("The success of discovering famotidine . . . was finding a compound that had high activity, few side effects, and lacked toxicity. . . . [T]he ordinary medicinal chemist would not have expected famotidine to have the 'most desirable combination of pharmacological properties' that it possesses."); *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc*., 364 F.Supp.2d 820, 908 (S.D. Ind. 2005) ("[S]uccess was not simply finding a compound as active as clozapine . . . . Here, the ordinary medicinal chemist . . . would not have expected olanzapine to have the highly desirable combination of pharmacological properties that it possesses.").

[1956] *Knoll Pharm. Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004); *Eli Lilly*, 364 F.Supp.2d at 908.

[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 ("Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were

In an obviousness determination, any objective indicia of nonobviousness must be taken into account.[1959] An objective indicium is any "event[] proved to have actually happened in the real world" that evidences the nonobvious nature of the invention.[1960] The existence of an enduring, unmet need, difficulties encountered by those skilled in the field, unexpected or surprising results, expressions of skepticism, industry praise, commercial success, and copying are classical indicia of nonobviousness.[1961] These factual inquiries "guard against slipping into use of hindsight,"[1962] and "may often be the most probative and cogent evidence of nonobviousness."[1963]

Also, as with assertions of anticipation, in order for an invention to be obvious, it must have been fully "in possession" of the public—which requires that the claimed invention have been enabled.[1964]

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unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 275 F.2d [952,] 955 [(C.C.P.A. 1960)], where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was 'particularly expected' that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant 'established a substantial record of unpredictability vis-à-vis a highly significant combination of properties.'").

[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).

[1960] *Panduit Corp. v. Dennison Mfg. Co*., 810 F.2d 1561, 1569 (Fed. Cir. 1987).

[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 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.

[1962] *Graham*, 383 U.S. at 36.

[1963] *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)).

[1964] *In re Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005) ("[I]n order to render an invention unpatentable for obviousness, the prior art must enable a person of ordinary skill to make and use the invention."); *In re Hoeksema*, 399 F.2d 269, 274 (C.C.P.A. 1968) ("[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public.").

A element-by-element analysis, identifying each limitation of each asserted claim that is absent from the prior art, is provided below, and also provided at Exhibit D. The contentions below are incorporated by reference into Exhibit D, and vice-versa.

a) General Overview

Defendants fail to provide a single prior art reference that discloses administration of the recited composition of EPA ethyl (in the recited purity) to the very-high TG patient population (≥500 mg/dL) and the resulting lipid effects. Instead, they rely on a large number of studies, many of which are not placebo controlled, which administer EPA, DHA, or both, in varying degrees of purity, in a wide range of doses and administration periods, to subjects who have baseline TG levels lower than 500 mg/dL and in many cases significantly lower. The importance of a placebo-controlled study cannot be overstated. Randomized, double-blind placebo controlled studies are considered the "gold standard" of clinical studies. Studies involving the administration of fish oils or omega-3 fatty acids which are not placebo controlled cannot distinguish between the effect of the placebo from that of the active agent. Studies which administer mixtures enriched for either EPA or DHA are not suitable for evaluating the independent effects of EPA and DHA.[1965] Inconsistency in dosages and administration periods and variations in the administered fatty acid compositions also complicate the interpretation of the results and limit the application of these studies.

Defendants also rely on the ANCHOR study to argue that Amarin's use of "patients with very high TGs together with patients with high and borderline high TGs indicates that there is no medical difference in responsiveness to treatment among the groups of people."[1966] Defendants

[1965] Mori 2006 at 96.

[1966] Defendants' Joint Invalidity Contentions at 533 (*see* FN 96).

mischaracterize the ANCHOR study. The ANCHOR study was a multi-center, placebo-controlled, randomized, double-blind, 12-week pivotal Phase 3 study on the effects of Vascepa in patients with high triglycerides (≥200 mg/dL and <500 mg/dL) who were also on statin therapy. Defendants point to the reported "Min-max" TG levels, 157-782 mg/dL, for the AMR101 4g daily group to argue that Amarin used very-high TG patients with high and borderline-high TG patients. However, the mean TG level for this same group, 281.1 mg/dL, makes it clear that almost all of the 233 patients in this group had baseline TG values well below 500 mg/dL.[1967] In addition, the mean baseline TG values for the Placebo and AMR101 2g daily groups were reported as 270.6 mg/dL and 270.2 mg/dL, respectively. Further, Amarin did *not* attempt to use the results of ANCHOR to predict lipid effects in the very high TG patient population. Neither a person of ordinary skill, nor the FDA, would attempt to draw conclusions or gain insight into the very high TG patient population from the ANCHOR trial. In fact, Amarin simultaneously (to ANCHOR) conducted an independent study with Vascepa in patients with very high TG levels. Contrary to Defendants' assertion, the ANCHOR study does *not* indicate that there is no medical difference in responsiveness to treatment between the very-high TG patient population and lower TG patient populations merely because there was possibly one patient with baseline TG levels of at least 500 mg/dL.

As discussed above in Section III, patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high TGs from a clinical, regulatory, and therapeutic perspective.[1968] Clinically, the authoritative guidance to physicians

[1967] FDA Briefing Document, Oct. 16, 2013 at pg. 26 (The mean baseline TG value for the placebo group was 270.6 mg/dL, AMR101 2g group was 270.2 mg/dL, and AMR101 4g group was 281.1 mg/dL. While there may have been a few patients with TG> 500mg/dL in the AMR101 4g group, it is clear that the overwhelming majority had baseline TG values < 500 mg/dL).

[1968] *See* Bays Jan. 8, 2012 Decl., ¶ 20.

on the treatment of lipid disorders throughout the last decade, the Adult Treatment Panel III (ATP-III) divided hypertriglyceridemic patients into three groups: normal/borderline high TG; high TG; and very high TG. The primary risk faced by borderline-high and high TG patients was atherosclerosis, while the primary risk faced by very-high TG patients was acute pancreatitis. Therefore, the primary focus of treatment, as described by the ATP III, for borderline-high and high TG patients was to lower LDL-C levels. In contrast, the priority for very-high TG patients was TG reduction. This distinction between patients with borderline-high/high TG levels and patients with very high TG levels is also observed on the regulatory level. The FDA recognized the different clinical status of the very-high TG population by approving some drugs specifically for the very-high TG group without granting treatment indications for the borderline-high or high TG populations (i.e. Lovaza/Omacor).[1969]

Finally, from a therapeutic standpoint, a person of ordinary skill understood that the effects of lipid-lowering therapies on lipid parameters, such as LDL-C, varied depending on the patient's baseline TG level. Fibrates and prescription omega-3 therapies (two well-known classes of drugs used to treat patient with very-high TGs to lower TG levels at the time of the invention), for example, exhibit different effects on LDL-C levels, depending on the baseline TG level of the patient receiving treatment.

Fibrates lower both TGs and LDL-C in normal and borderline-high TG patients, but *increase* LDL-C in very-high TG patients.[1970] The fibrate, Tricor (fenofibrate), for example,

[1969] *See* Bays Jan. 8, 2012 Decl., ¶ 22.

[1970] *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).

decreased LDL-C significantly in both patients with normal baseline TG values (about 31%)[1971] and high baseline TG values (mean baseline TG value of 231.9 mg/dL) (about 20%).[1972] In patients approaching very-high TGs levels (mean baseline TG value of 432 mg/dL), a non-significant increase in LDL-C was observed.[1973] In patients with very-high TGs (mean baseline TG = 726 mg/dL), a significant increase in LDL-C was observed (about 45%).[1974] Similar results were seen with the administration of Lopid (gemfibrozil).[1975] The differing effects of fibrates, such as Tricor, on TG, LDL-C , HDL-C and Total-C based on baseline TG values demonstrates how a person of ordinary skill at the time of the invention would have understood that one could not simply assume that an observed effect of a TG-lowering agent on lipid parameters in patients with normal, borderline-high or high TG levels would be the same in patients with very-high TG levels (at least 500 mg/dL) compared to a patient with high or borderline-high TG levels (150-499 mg/dL). As illustrated in the table, below, patients with normal or high baseline TG levels experience reduced LDL-C levels upon treatment with a TG-reducing agent such as the fibrate, Tricor. Patients approaching very high TG levels (mean baseline TG level of 432 mg/dL) and patients with very high TG levels (mean baseline TG level of 726 mg/dL) experience significantly increased LDL-C levels.

| **Fibrate** | **Mean Baseline TG Value** | **TG** | **LDL-C** | **HDL-C** | **Total-C** |
|---|---|---|---|---|---|

[1971] Tricor®, Physicians' Desk Reference 502-505 (62d ed. 2008).

[1972] *Id.*

[1973] *Id. See also*, Trilipix Label at 27.

[1974] *Id. See also*, Trilipix Label at 27.

[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 [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

Fibrates and prescription Omega-3 therapies demonstrate that one could not simply assume that a lipid lowering agent would have the same effect in a patient with very-high TG levels (≥500 mg/dL) as a patient with borderline-high or high TG levels (150-499 mg/dL). They also demonstrate that one of ordinary skill would not expect to see an increase in LDL-C when the normal, borderline-high or high TG patient populations were administered omega-3 fatty acids. As discussed in Section III, the increase in LDL-C for very-high TG patients was expected as a natural consequence of lowering TGs. A person of ordinary skill would have considered the rise in LDL-C to be a direct consequence of TG lowering through increased VLDL particle conversion.[1981] Because normal to high TG patients did not have the large backlog of VLDL particles that very high TG patients have, a person of ordinary skill did not expect LDL-C to increase in normal to high TG patients. It was also well known that the degree of LDL-C elevation observed with prescription omega-3 fatty acids, such as Lovaza/Omacor, was linked to baseline TG levels; that LDL-C levels increased the most in patients with the highest baseline TG levels[1982] and did not increase for patients with lower TG levels. Therefore, the prior art defendants rely upon to show that EPA did *not* increase LDL-C levels in normal, borderline-high or high TG patients was *expected*.

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acids decrease the total cholesterol (TC) carried by atherogenic lipoproteins, as reflected by decreased non-HDL-C levels (TC minus HDL-C.)"

[1981] 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.").

[1982] Bays 2008 I at 400-402.

Defendants contend that "a composition and its properties are inseparable, and therefore do not impart any additional patentability," and that "all of the limitations regarding the properties of the ethyl EPA compound identified in the claims of the '399 patent are inherent to the compound when administered to a human subject."[1983] Inherency may not supply a missing claim limitation in an obviousness analysis unless the inherency would have been obvious to one of ordinary skill in the art.[1984] Obviousness is based on what is *known* in the art at the time of the invention.[1985] It was not known or reasonably expected at the time of the claimed invention that purified EPA, when administered to patients with very-high TG levels (≥500 mg/dL), would not substantially increase LDL-C or would reduce Apo-B. Nor was EPA's effect on LDL-C and Apo-B necessarily present, or the natural result of the combination of elements explicitly disclosed by the prior art.[1986] Therefore, inherency does not supply the missing claim elements in the prior art cited by Defendants.

Defendants argue that the claims of the '399 patent which contain "a limiting clause, such as 'to effect' or 'is effective to,'" simply express the intended result of a process step positively recited and therefore are not elements.[1987] This is incorrect. "There is nothing inherently wrong

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[1983] Defendants' Joint Invalidity Contentions at 534.

[1984] *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).

[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 Invalidity Contentions at 535.

with defining some part of an invention in functional terms."[1988] When a clause "states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention."[1989] The claim term "to effect" acts as a positive limitation if the term represents "unexpected and improved effects of administration of the claimed compound."[1990] In addition, the elements represent unexpected and improved effects of administration of purified EPA, because a person of ordinary skill would not have expected no substantial increase in LDL-C or reduction in Apo-B when administering EPA to treat severe hypertriglyceridemia. Therefore, the requirements for no substantial increase in LDL-C and reduction in Apo-B must be accorded patentable weight.

b) Identification of Claim Elements Absent from Each Item of Prior Art

Plaintiffs identify each limitation of each asserted claim that Plaintiffs believe is absent. Where a limitation is absent from any Independent Claim, that limitation is absent from all asserted claims, and that analysis is incorporated by reference into each dependent claim. For any reference, the fact that Plaintiffs do not list a particular limitation as absent from the asserted claims is not a concession that such limitation is present in the reference. By discussing Defendants' analysis of the "limitations" in the claims, Plaintiffs do not concede that Defendants have appropriately divided the claim language for any purpose.

(1) WO '118

WO '118 discloses a composition containing EPA-E for preventing the occurrence of cardiovascular events in multiple risk patients.

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[1988] *See* MPEP 2173.05(g) (citing *In re Swinehart*, 439 F.2d 210 (CCPA 1971 )).

[1989] Hoffer v. Microsoft Corp., 405 F.3d 1326, 1329 (Fed. Cir. 2005).

[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).

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '118 disclose or suggest elements of the '399 Claims. The cited portions of WO '118 do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of WO '118 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), WO '118 does not disclose or suggest a first group of subjects with the recited very high TG level. WO '118 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or dosage. The cited portions of WO '118 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(2) WO '900

WO '900 describes methods for obtaining EPA-rich compositions.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of WO '900 disclose or suggest elements of the '399 Claims. The cited portions of WO '900 do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of WO '900 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. The cited portions of WO '900 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), WO '900 does not disclose or suggest a subject with the recited very high TG level. WO '900 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. WO '900 also does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C

levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(3) Contacos

Contacos describes a study designed to determine the safety and efficacy of a statin (pravastatin) combined with fish oil either alone or in combination, for the management of patients with mixed hyperlipidemia. Contacos does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Contacos disclose or suggest elements of the '399 Claims. The cited portions of Contacos do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Contacos further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions, dosage, or administration period. The cited portions of Contacos further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a

second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Contacos does not disclose or suggest a subject with the recited very high TG level. Contacos also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Contacos also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(4) Grimsgaard

Grimsgaard conducted a double-blind, randomized, placebo-controlled, parallel design intervention study to evaluate the dietary supplementation with EPA or DHA on serum lipids, apolipoproteins, and serum phospholipid fatty acid composition in subjects with normal TG levels.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Grimsgaard disclose or suggest elements of the '399 Claims. The cited portions of Grimsgaard do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Grimsgaard further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Grimsgaard does not disclose or suggest a first group of subjects with the recited very high TG level. Grimsgaard also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or administration period. The cited portions of Grimsgaard further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects with the claimed TG levels having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(5) Hayashi

Hayashi is directed to administration of ethyl icosapentate 1800mg (6 capsules) daily for 8 weeks. The purity of the composition is not reported. The study was not placebo controlled and was conducted in 28 patients with familial combined hyperlipidemia and a serum tryglceride concentration higher than 150 mg/dl or serum total cholestorol concentration higher than 220 mg/dl.

The portions of Hayashi cited by Defendants do not disclose or suggest elements of the '399 patent claims. For example, the cited portions of Hayashi do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. Figure 2 demonstrates that no subject had a TG level above 400 mg/dl. The cited portions of Hayahsi further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Hayashi further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very

high TG levels.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Hayashi does not disclose or suggest a first group of subjects with the recited very high TG level. Hayashi also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Hayashi also does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(6) Katayama

Katayama was directed to an investigation of the safety and efficacy of Epadel during long term treatment in patients with hyperlipidemia that was not placebo controlled. Notably, Katayama did not disclose or suggest any LDL-C related data or describe any LDL-C effects and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Katayama disclose or suggest elements of the '399 Claims. The cited portions of Katayama do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Katayama further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Katayama further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Katayama does not disclose or suggest a first group of subjects with the recited very high TG level. Katayama also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Katayama also does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to

the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(7) Leigh-Firbank

Leigh-Firbank studied the impact of fish-oil intervention on LDL oxidation, particle density and concentration in subjects with an atherogenic lipoprotein phenotype. Leigh-Firbank does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Leigh-Firbank disclose or suggest elements of the '399 Claims. The cited portions of Leigh-Firbank do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Leigh-Firbank further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions, dosage, or administration period. The cited portions of Leigh-Firbank further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Leigh-Firbank does not disclose or suggest a subject with the recited very high TG level. Leigh-Firbank also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Leigh-Firbank also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a

second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(8) Lovaza PDR

The Lovaza PDR is the Physicians' Desk Reference describing Lovaza.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Lovaza PDR disclose or suggest elements of the '399 Claims. The cited portions of the Lovaza PDR do not disclose or suggest these elements at least because they do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or administration period. The cited portions of the Lovaza PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of

subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), the Lovaza PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Lovaza PDR also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effect. With respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claim 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(9) Maki

Maki administered 1.52g/day DHA supplements to patients with below-average levels of HDL-C. Maki does not administer EPA of the purity recited in the claims.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Maki disclose or suggest elements of the '399 Claims. The cited portions of Maki do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Maki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions, dosage, or administration period. The cited portions of Maki further do not disclose or suggest a

method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Maki does not disclose or suggest a subject with the recited very high TG level. Maki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions, dosage, or administration period. Maki also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical

composition to effect the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(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 '399 Claims. The cited portions of Matsuzawa do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Matsuzawa further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Matsuzawa further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Matsuzawa does not disclose or suggest a first group of subjects 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 also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(11) Mori 2000

Mori 2000 aimed to determine whether EPA and DHA have differential effects on serum lipids and lipoproteins, glucose and insulin in humans.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2000 disclose or suggest elements of the '399 Claims. The cited portions of Mori 2000 do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Mori 2000 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second

group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Mori 2000 does not disclose or suggest a first group of subjects with the recited very high TG level. Mori 2000 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or administration period. The cited portions of Mori 2000 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects with the claimed TG levels having the recited baseline LDL-C levels. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(12) Mori 2006

Mori 2006 is a review which reports data from clinical trials which compared the independent effects of EPA and DHA in individuals at increased risk of cardiovascular disease.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Mori 2006 disclose or suggest elements of the '399 Claims. The cited portions of Mori 2006 do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Mori 2006 further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. The cited portions of Mori 2006 further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Mori 2006 does not disclose or suggest a subject with the recited very high TG level. Mori 2006 also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage or administration period. Mori 2006 also does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this

reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(13) Nozaki

Nozaki is directed to administration of 2.7 g ethyl icosapentate per day for 6 months. The purity of the composition is reported as 90%. The study was not placebo controlled and was conducted in 14 hypercholesterolemic subjects. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population.

The portions of Nozaki cited by Defendants do not disclose or suggest elements of the '399 patent claims. For example, the cited portions of Nozaki do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in a subject with the recited very high TG levels.

Defendants assert that certain cited sections of Nozaki disclose or suggest elements of the '399 Claims. The cited portions of Nozaki do not disclose or suggest these elements at least

because they do not disclose or suggest administration of EPA with the recited purity to a subject with the recited very high TG levels who does not receive concurrent lipid altering therapy. The cited portions of Nozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Nozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Nozaki does not disclose or suggest a first group of subjects with the recited very high TG level. Nozaki also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Nozaki also does not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects based on a comparison to the second group of subjects. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects based on a comparison to the second group of subjects.

(14) Omacor PDR

The Omacor PDR is the Physicians' Desk Reference describing Omacor.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of the Omacor PDR disclose or suggest elements of the '399 Claims. The cited portions of the Omacor PDR do not disclose or suggest these elements at least because they do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acids compositions or administration period. The cited portions of the Omacor PDR further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), the Omacor PDR does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claims 6 and 7, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited TG and LDL-C effect. With respect to Claim 8, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in Apolipoprotein B. With respect to Claim 9, this reference fails to disclose or suggest the administration of the claimed pharmaceutical composition to effect the recited reduction in VLDL-C.

(15) Satoh

Satoh administered 1.8g/day of >98% EPA to patients in order to measure the effects of PEA on C-reactive protein and examine how alteration of lipoprotein profile by EPA affects systemic inflammation.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Satoh disclose or suggest elements of the '399 Claims. The cited portions of Satoh do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Satoh further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Satoh further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Satoh does not disclose or suggest a first group of subjects with the recited very high TG level. Satoh also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid composition or dosage. The cited portions of Satoh further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects with the claimed TG levels having the recited baseline LDL-C levels.

With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(16) Shinozaki

Shinozaki studied the long-term effect of EPA on serum levels of Lipoprotein (a) and lipids such as triglycerides, total cholesterol, and low density lipoprotein particles.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Shinozaki disclose or suggest elements of the '399 Claims. The cited portions of Shinozaki do not disclose or suggest these elements at least because they do not disclose or suggest a first group of subjects with the recited very high TG levels. The cited portions of Shinozaki further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Shinozaki does not disclose or suggest a first group of subjects with the recited very high TG level. Shinozaki also does not disclose or suggest the claimed pharmaceutical composition with the

recited fatty acid dosage. The cited portions of Shinozaki further do not disclose or suggest a method to effect the recited TG reduction without substantially increasing LDL-C in the first group of subjects with the recited very high TG level, based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 2, this reference does not disclose or suggest administration to the subject 1 to 4 times per day. With respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

(17) Takaku

Takaku administered Epadel to patients with hyperlipaemia in order to study its long-term use and was not placebo controlled.

In its Local Patent Rule 1-8(d) chart, Defendants assert that certain cited sections of Takaku disclose or suggest elements of the '399 Claims. The cited portions of Takaku do not disclose or suggest these elements at least because they do not disclose or suggest a first group of

subjects with the recited very high TG levels. The cited portions of Takaku further do not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. The cited portions of Takaku further do not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

With respect to Claim 1 of the '399 Patent (and therefore all asserted claims), Takaku does not disclose or suggest a first group of subjects with the recited very high TG level. Takaku also does not disclose or suggest the claimed pharmaceutical composition with the recited fatty acid compositions or dosage. Takaku also does not disclose or suggest a method of administering the claimed pharmaceutical composition to effect the recited TG reduction without substantially increasing LDL-C based on a comparison to a second group of subjects with the recited very high TG levels who have not received the pharmaceutical composition and a concurrent lipid altering therapy.

Further, with respect to Claim 4, this reference fails to disclose or suggest the first and second groups of subjects having the recited baseline LDL-C levels. With respect to Claim 5, this reference does not disclose or suggest the first and second groups of subjects having the recited baseline lipid values. With respect to Claims 6 and 7, this reference fails to disclose or suggest the recited TG and LDL-C effect in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level. With respect to Claim 8, this reference fails to disclose or suggest the recited reduction in Apolipoprotein B in the first group of subjects with the claimed TG levels based on a comparison

to the second group of subjects with the claimed TG level. With respect to Claim 9, this reference fails to disclose or suggest the recited reduction in VLDL-C in the first group of subjects with the claimed TG levels based on a comparison to the second group of subjects with the claimed TG level.

c) The Prior Art Does Not Render the Claims Obvious

Defendants have not identified by clear and convincing evidence that the asserted claims of the '399 Patent would have been *prima facie* obvious in light of the references cited, either alone or in combination. As described above, none of the references discloses all of the elements in any of the asserted claims. Defendants chart a laundry list of 66 separate references, without explanation, and argue they somehow must be combined to render obvious the asserted claims. Where Defendants have failed to make disclosures with the specificity required by Local Patent Rule 1-8(d), it has failed to put Plaintiffs on notice of how these references allegedly disclose the claim elements at issue.

Defendants' contentions fail to disclose each and every element of the claims of the '399 patent. Specifically, Defendants do not contend that the relied upon references disclose the following elements of Claim 1 (and therefore Claims 2-9): *administering the claimed pharmaceutical composition to the recited first group of subjects to effect a reduction in triglycerides without substantially increasing LDL-C based upon a comparison to a second group of subjects having a median fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl who have not received the pharmaceutical composition and a concurrent lipid altering therapy*. Therefore, Defendants' prior art combinations cannot render the claims *prima facie* obvious.

Facts supporting the non-obviousness of the claims of the '399 patent are discussed in detail below. The objective indicia discussed in Section V.O further demonstrate that the '399

Patent is not obvious. In short, Defendants have not met their burden of showing that the claims would have been obvious.

(1) Defendants Do Not Demonstrate that the Independent Claim of the '399 Patent Would Have Been Obvious

(a) Defendants Do Not Demonstrate that a Person of Ordinary Skill in the Art Would Have Had Any Reason to Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

(i) The '399 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, Further in View of Nozaki and/or Hayashi and Further in View of Leigh-Firbank and/or Mori 2000

With respect to the '399 Patent, Defendants present a combination of seven references: "the Omacor PDR/Lovaza PDR in combination with the known clinical benefits of administering pure EPA as evidenced by Katayama and/or Matsuzawa, further in view of Nozaki and/or Hayashi and further in view of Leigh-Firbank and/or Mori 2000."[1991] 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

[1991] Defendants' Joint Invalidity Contentions at 528.

combining these references.[1992, 1993] 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.[1994] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[1995] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all

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[1992] Defendants' bare assertion that the asserted claims are obvious "in view of one or more of Omacor or Lovaza (as described in the references cited above in section V.B.2 in view of, at least, the references cited in V.B.3 and 4, including, the '954 publication, WO '900, WO '118, Ando, Grimsgaard, Hayashi, Katayama, Matsuzawa, Mataki, Mori 2000, Nakamura, Nozaki, Okumura, Park, Saito 1998, Saito 2008 Satoh, Shinozaki, Takaku, Yokoyama 2003, Yokoyama 2007, Calabresi, Chan 2002, Chan 2003, Contacos, Geppert, Kelley, Leigh-Firbank, Maki, Mori 2006, Rambjør, Sanders or Theobald," similarly fails to meet the disclosure requirements of the Nevada Local Patent Rules, and fails to provide any motivation to combine these references. *See* Defendants' Joint Invalidity Contentions at 528.

[1993] Defendants' bare assertion that "the motivation or reason to combine or modify the prior art to create invalidating combinations under 35 U.S.C. §103 can be found in the references identified above in Section III.C," and that "[c]ommon sense, design incentives. Market forces, and the background knowledge possessed by a person having ordinary skill in the art provide the reasons or rationales for combining the teachings of multiple references or modifying references to render obvious the claimed inventions of the asserted claims," fails to meet the disclosure requirements of the Nevada Local Patent Rules. *See* Defendants' Joint Invalidity Contentions at 526.

[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").

that it teaches.[1996] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Lovaza PDR fails to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition containing the claimed fatty acid compositions or administration period. The Lovaza PDR further does not disclose a method to effect the specified TG reduction without substantially increasing LDL-C. Indeed, the Lovaza PDR discloses the exact opposite. The EPA/DHA composition of Lovaza causes a significant increase in LDL-C levels in the very high TG patient population, for whom the product is indicated. At most, the Lovaza PDR discloses administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375 mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (≥ 500 mg/dL) TG levels.

The proposed combinations do not render the independent claim of the '399 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, Mori 2000, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[1997]

The analysis of the independent claim of the '399 Patent is incorporated into all asserted claims that depend from this Claim.

***(a)*** A Person of Ordinary Skill Would Not Have Been Motivated to

[1996] *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011)

[1997] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

Replace the Mixed Fish Oil Active Ingredient in Lovaza with Pure EPA

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '399 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Katayama 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.[1998] 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

[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.)

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 '399 patent, a person of ordinary skill in the art would have expected an *increase* in LDL-C for very-high TG patients receiving a TG-lowering agent, as a natural consequence of lowering TGs. This pattern had been demonstrated for both fibrates and fish oils and was understood as a direct consequence of TG lowering through increased VLDL particle conversion.

Defendants argue that these studies disclose known "clinical benefits" of administering pure EPA, lowering triglycerides without raising LDL-C.[1999] This is an incorrect characterization of these two studies. Katayama and Matsuzawa both were only designed to confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and TG levels. They do just that. They do not discuss any purported "benefits" observed related to LDL-C. Defendants' selective citation of LDL-C data from these references represents the improper use of hindsight bias. A person of ordinary skill would understand the focus of Katayama and Matsuzawa to be TG and total cholesterol effects and not LDL-C levels, and would not draw conclusions regarding LDL-C from these studies. Indeed, Katayama does not mention LDL-C levels at all. Defendants' characterization of Katayama and Matsuzawa as disclosing the lowering of TG levels without increasing LDL-C to be a "clinical benefit" is incorrect.[2000] The references don't disclose or suggest that the LDL-C results obtained were a clinical benefit, nor

[1999] Defendants' Joint Invalidity Contentions at 528-29.

[2000] Defendants' Joint Invalidity Contentions at 528-29.

would a person of ordinary skill view these references as teaching such a benefit for very-high TG patients.

Further, both Katayama and Matsuzawa administered only EPA and studied its lipid effects. These studies fail to provide a head to head comparison of EPA versus DHA. Therefore, a person of ordinary skill in the art would not rely on Katayama or Matsuzawa to draw any conclusions related to possible differences between the lipid effects of EPA and DHA.

In addition, Katayama and Matsuzawa do not disclose the purity of the Epadel used. The purity of Epadel has varied over time and across different formulations of the product, therefore it is difficult to determine the purity of the version of Epadel used unless it is specified by the disclosure. One cannot simply rely on the fact that Epadel was administered and assume that the composition comprised at least about 96%, by weight of all fatty acids present, EPA, and substantially no DHA, as required by the asserted claims. Defendants fail to provide a reference disclosing the purity of the form of Epadel used in the Katayama and Matsuzawa studies. Nishikawa,[2001] published in 1997, discloses a form of Epadel that was a 91% E-EPA preparation. Nishikawa reflects that versions of Epadel used in some clinical studies do not have the requisite purity.[2002]

Further, Katayama and Matsuzawa were small studies conducted in only Japanese patients. These studies would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In

[2001] Nishikawa et al., *Effects of Eicosapentaenoic Acid (EPA) on Prostacyclin Production in Diabetics: GC/MS Analysis of $PGI_2$ and $PGI_3$ Levels*, 19 METHODS FIND EXP CLIN PHARMACOL. 429 (1997).

[2002] *See also*, Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

fact, Yokoyama 2007 (cited in Defendants' contentions) states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2003] The Japanese diet comprises between 8 and 15 times more EPA and DHA than the typical Western Diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Defendants rely on Katayama to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[2004] However, Katayama was directed to an investigation of the safety and efficacy of Epadel during long-term treatment in patients with hyperlipidemia.[2005] Katayama does not disclose *any* LDL-C related data or describe *any* LDL-C effects, and a person of ordinary skill would not understand that reference to provide any such disclosure. The only results disclosed by Katayama were a significant reduction in TGs and total cholesterol when Epadel (EPA of undisclosed purity) was administered to patients with borderline-high to high TG levels, and its safety for long term use in this patient population.[2006] In addition to Katayama's lack of disclosure regarding LDL-C, Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Katayama with the Lovaza PDR.

[2003] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2004] Defendants' Joint Invalidity Contentions at 528.

[2005] Katayama at 2.

[2006] *Id.* at 16.

Defendants similarly rely on Matsuzawa to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C."[2007] However, Matsuzawa included 26 participants, of whom 23 were adopted for the evaluation of overall safety, 22 were adopted for the evaluation of usefulness, 20 were adopted for evaluation of general improvement, 15 were adopted for improvement in serum total cholesterol levels, and 13 were evaluated for improvement in serum triglycerides levels.[2008] It is unclear which of the 26 patients were included in each separate evaluation; therefore one cannot determine the baseline lipid characteristics for each subset of patients evaluated. Further, the small sample size and lack of a placebo control makes it less likely that the results of this study can be generalized as an effect on any population as a whole and provides no insight with respect to the very-high TG patient population.

Matsuzawa discloses that 3 of the 26 participants had 400 mg/dL < TG < 1000 mg/dL, and one participant with TG levels > 1,000 mg/dL.[2009] However, when analyzing the lipid impact of Epadel, Matsuzawa excluded the patient with a TG level greater than 1,000 mg/dL because he was a "heavy drinker" and the "effect of alcohol made it impossible to assess triglyceride levels."[2010] Fig. 4, which depicts the changes in serum triglycerides, shows that the mean triglycerides of the 12 patients with TG greater than 150 mg/dL was well below 500 mg/dL. Furthermore, as shown in Table 4, patients with TG levels above 500 mg/dL (other than the excluded patient who had TG above 1,000 mg/dL) were not treated in the study with EPA (of undisclosed purity). The identification of three patients with TG levels between 400 and less

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[2007] Defendants' Joint Invalidity Contentions at 528.

[2008] Matsuzawa at 7 and 19.

[2009] *Id.* at 23.

[2010] *Id.* at 10.

than 1,000 mg/dL does not disclose a patient with TG levels above 500 mg/dl, and a person of ordinary skill would not understand that the reference makes any such disclosure. As discussed above, one of ordinary skill in the art would not expect LDL-C to increase in a patient with TG less than 500 mg/dL upon treatment with a TG-lowering agent. Matsuzawa provides no evidence to the contrary.

Matsuzawa demonstrated mixed results related to LDL-C over time, at first showing a 2% decrease, and then a 1% increase in LDL-C by the end of 52 weeks.[2011] The disclosure further reflects that the 4 patients with serum triglyceride levels of at least 400 mg/dL were excluded from the LDL-C results because the Friedewald's Equation was used to calculate LDL-C levels. The Friedewald's Equation cannot be used for patients with triglyceride levels of at least 400 mg/dL. Therefore, the LDL-C results only reflect the LDL-C changes in patients with triglyceride levels below 400 mg/dL. Matsuzawa fails to provide any information to a person of ordinary skill regarding the LDL-C effect in the very-high TG population. A person of ordinary skill in the art, however, would have expected the same treatment in patients with very high TG levels to produce a substantial increase in LDL-C. In addition, Matsuzawa acknowledges that there have been conflicting results related to the LDL-C impact of EPA preparations that lowered triglyceride levels.[2012] At best, Matsuzawa demonstrates the uncertainty and confusion related to the LDL-C effect EPA had on patients with hyperlipidemia. Further, Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine the composition disclosed in Matsuzawa with the Lovaza PDR.

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[2011] *Id.* at 11.

[2012] *Id.* at 15. Matsuzawa suggests the conflicting results are due to differences in the EPA content of the EPA preparation administered. However, Matsuzawa fails to identify the specific conflicting studies, disclose the specific compositions used, or identify the patient populations were observed.

Therefore, Katayama and Matsuzawa fail to substantiate Defendants' assertion that compositions comprising EPA as recited in the asserted claims lowers triglycerides without substantially increasing LDL-C. Further, other studies cited by Defendants suggest that EPA increases LDL-C.[2013] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000 or reasonably expected that such a combination would successfully yield the asserted claims of the '399 patent.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '399 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population.

[2013] *See, e.g.*, Rambjor.

Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[2014] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[2015] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

[2014] Nozaki at 256.

[2015] Hayashi at 26, Table I.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes. The Japanese consume a higher amount of EPA and DHA in their diets than Western populations. In fact, Defendants' own reference states that the results from studies where the patient population is exclusively Japanese cannot be generalized to other populations.[2016] The Japanese diet comprises between 8 and 15 times more EPA and DHA than typical the typical Western diet. The Western diet typically consists of higher amounts of polyunsaturated omega-6 fatty acids and saturated fatty acids. Therefore, a person of ordinary skill would understand that the Japanese respond differently to lipid lowering agents than Westerners.

Further, Defendants have failed to offer a purported combination of references as part of their obviousness contentions that include Nozaki and Hayashi. Similarly, they fail to offer any motivation to combine Nozaki and Hayashi with the other references of their purported obviousness combinations. Therefore, Defendants should be precluded from relying on these references.

(iii) Leigh-Firbank and/or Mori 2000 Do Not Disclose Purported Knowledge that DHA was Responsible for the Increase in LDL-C

Defendants assert, incorrectly, that "it was known in the art as of February 2009 that administration of DHA (alone or in a mixture) resulted in the negative effect of increasing LDL-C levels."[2017] Defendants' caveat of DHA being "alone or in a mixture" is telling that it was *not*

[2016] Yokoyama 2007 at 1097 ("Because our population was exclusively Japanese, we cannot generalise our results to other populations.").

[2017] Defendants' Joint Invalidity Contentions at 532.

known that DHA alone resulted in an increase in LDL-C levels. Further, the prior art Defendants rely upon to support this statement does not categorize the increase in LDL-C as a "negative effect" in light of the overall impact of the disclosed composition on all lipid parameters. Further, the patients in Leigh Firbank and Mori 2000 had normal to high baseline TG levels. As discussed above in Section III, a person of ordinary skill would not expect the same LDL-C effect in patients with lower baseline TG levels—the subjects of Leigh-Firbank and Mori 2000—as in very-high TG patients because patients with higher TG levels had different lipid responses compared to patients with lower TG levels. Patients with very-high TG levels were considered fundamentally different from patients with borderline-high or high triglycerides from a lipid chemistry, medical, clinical guideline, regulatory, and therapeutic standpoint. Instead, a person of ordinary skill in the art would have expected that fish oils (and other TG lowering agents) would not increase LDL-C substantially in patients with normal to borderline high TG levels, but would substantially increase LDL-C in patients with very high TG levels.

Defendants rely upon Leigh-Firbank to demonstrate that it was known that "DHA was responsible for the increase in LDL-C levels." Leigh-Firbank, however, administered fish oil, comprising 1.67 g of EPA and 1.34 g of DHA per day, for six weeks, to patients with triglyceride levels between 133 mg/dL and 354 mg/dL. Leigh-Firbank does not evaluate the effect of either EPA or DHA alone because it did not disclose the administration of EPA or DHA alone. A person of ordinary skill would similarly understand that Leigh-Firbank does not offer any disclosure regarding the effect of EPA and DHA separately or gain any understanding of the separate impact of DHA or EPA on any lipid parameter. Mori 2006 (also cited by defendants) acknowledges that EPA- and DHA-enriched oils, which are contaminated with other saturated and polyunsaturated fatty acids, are not suitable for evaluating the independent effects of EPA

and DHA.[2018] A person of ordinary skill would understand that studies directed to EPA and DHA-enriched oils are not indicative or predictive of the impact of the EPA or DHA alone on lipid parameters. Defendants' own prior art refutes the validity of the results disclosed by Leigh-Firbank, because purified EPA and DHA were not administered separately.

Leigh-Firbank is a poor quality study. Leigh-Firbank makes conclusion on independent effects of EPA and DHA individually, even though it administered a combination of EPA and DHA, not EPA alone and DHA alone. The error in this approach is evident from the conclusions of Leigh-Firbank itself. For example, Leigh-Firbank concludes that changes in platelet phospholipid EPA were *independently* associated with the decrease in fasting TGs,[2019] and DHA is *not* associated with decreases in fasting TGs. This is incorrect and inconsistent with the state of the art and numerous publications cited by Defendants.[2020] It is widely accepted that DHA also has a hypotriglyceridemic effect.

Mori 2000 compared the administration of 4g daily of EPA, DHA, or olive oil to patients with borderline-high TG levels for 6 weeks. Although Mori 2000 discloses an increase in LDL-C for patients administered DHA, it also teaches that DHA is preferable to EPA—thus teaching away from the claimed invention. "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant."[2021] Although teaching away is fact-dependent, "in general, a reference will teach

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[2018] Mori 2006 at 96.

[2019] Leigh-Firbank at 440.

[2020] *See, e.g.* Grimsgaard at 654.

[2021] *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994).

away if it suggests that the line of development flowing from the reference's disclosures is unlikely to be productive of the result sought by the applicant."[2022]

Mori 2000 concludes that the changes effected by DHA supplementation "may represent a more favorable lipid profile than after EPA supplementation."[2023] For example, it states that "DHA, but not EPA, improved serum lipid status, in particular a small increase in HDL cholesterol and a significant increase in the $HDL_2$-cholesterol subfraction, without adverse effects on fasting glucose concentrations."[2024] Mori 2000 also states that "[d]espite an increase in LDL cholesterol after DHA supplementation, LDL particle size increased—a finding that may be favorable."[2025] Therefore, based on the "favorable lipid profile" of DHA over EPA in Mori 2000, a person of ordinary skill would *not* have been motivated to use EPA to treat patients, the exact opposite of what Defendants argue in their contentions. Therefore, the art taught away from using purified EPA. At a minimum, the teachings of Mori 2000 provide reasons for favoring or selecting DHA over EPA and highlight Defendants' hindsight-driven focus on EPA, despite disclosed advantages of DHA. A person of ordinary skill would take into consideration the entire disclosure, including lipid effects other than LDL-C. Engaging in hindsight bias, Defendants ignore, without explanation, the other effects of DHA that a person of ordinary skill would consider. Defendants fail to identify any other basis upon which a person of ordinary skill would have sought to combine Mori 2000 with the Lovaza PDR.

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[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.").

[2023] Mori 2000 at 1092.

[2024] Mori 2000 at 1088.

[2025] Mori 2000 at 1092.

Therefore, Leigh-Firbank and Mori 2000 fail to substantiate Defendants' assertion that it was known that DHA alone was responsible for the increase in LDL-C levels. Further, Defendants ignore, without explanation, other studies that demonstrate that DHA decreases or has little effect on LDL-C levels.[2026] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Lovaza PDR with Katayama, Matsuzawa, Leigh-Firbank and/or Mori 2000.

(ii) The '399 Patent is not Obvious Over the Omacor PDR/Lovaza PDR, in Combination with Katayama and/or Matsuzawa, and/or Takaku, Further in View of Nozaki and/or Hayashi, and Further in View of Grimsgaard, Mori 2000 and/or Maki

With respect to the '399 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."[2027] 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

[2026] *See e.g.*, Grimsgaard; Agren; Conquer 1996; Nelson; Hamazaki; Woodman; Nestel; Childs.

[2027] Defendants' Joint Invalidity Contentions at 5029.

factual record.[2028] Defendants' unsupported cobbling of selective disclosures represents hindsight reconstruction.[2029] Defendants' contentions are no more than an assertion that certain claim elements were known in the prior art. Throughout their contentions, Defendants' selectively cite to data points in a reference without considering other disclosures or even the reference as a whole. Each reference, however, must be evaluated for all that it teaches.[2030] Accordingly, Defendants fail to meet their burden to establish *prima facie* obviousness.

The Omacor PDR and Lovaza PDR fail to disclose or even suggest the claimed method of reducing triglycerides in a subject with the claimed pharmaceutical composition with the recited fatty acid compositions or administration period. The Omacor PDR and Lovaza PDR further do not disclose a method to effect the claimed TG reduction without substantially increasing LDL-C. Indeed, the Omacor PDR and Lovaza PDR disclose the opposite: EPA/DHA causes a significant increase in LDL-C levels in a very high TG patient population, for whom the product (Lovaza/Omacor) is indicated. At most, the Omacor PDR and Lovaza PDR disclose administration of a prescription fish oil, a combination of approximately 465 mg EPA and 375

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[2028] *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).

[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)

mg DHA, as an adjunct to diet to reduce TG levels in adult patients with very-high (at least 500 mg/dL) TG levels. The proposed combinations do not render the independent claim of the '399 Patent obvious and Defendants' burden to prove otherwise is especially difficult because the PTO considered Matsuzawa, Katayama, and Mori 2000, Grimsgaard, Maki, and Lovaza (both generally and the Lovaza package insert specifically) during prosecution.[2031]

The analysis of the independent claim of the '399 Patent is incorporated into all asserted claims that depend from this Claim.

(a) A Person of Ordinary Skill Would Not Have Been Motivated to Replace the Mixed Fish Oil Active Ingredient in Omacor/Lovaza with EPA of the Claimed Purity

For an invention to be obvious, there must have been an "apparent reason" to make it. The subject matter of the '399 patent claims would not have been obvious in light of these references because a person of ordinary skill would not have been motivated to purify EPA or been able to reasonably expect that the claimed pharmaceutical composition would reduce TG levels without an increase in LDL-C levels.

(i) Grimsgaard, Katayama, Matsuzawa and/or Takaku Do Not Disclose Purported Known Clinical Benefits of Administering Pure EPA

Defendants rely on Grimsgaard, Katayama, Matsuzawa and/or Takaku to demonstrate the "known clinical benefits of administering pure EPA - lowering triglycerides without raising LDL-C." As discussed in Section V.D.3.c.1.a.i.a.i, incorporated herein by reference, Katayama

[2031] *See, e.g.*, *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012)(taking into account that "the examiner considered during prosecution all the prior art cited by [the defendants] against the claimed invention. Thus, the examiner found that the prior art applied in this case had not precluded patentability even before the clear and convincing standard came into play").

and Matsuzawa merely confirm the safety of long term treatment of Epadel and its ability to lower both serum total cholesterol and triglyceride levels. They do not discuss any purported "benefits" observed related to LDL-C. Katayama and Matsuzawa do not disclose or suggest that the LDL-C results obtained were a clinical benefit.

Defendants also rely on Grimsgaard to support their assertion that "administration of purified EPA-E reduced TG levels while minimally impacting the LDL-C levels."[2032] However, the results of Grimsgaard demonstrate that both EPA and DHA had no measureable impact on LDL-C levels, and in fact were indistinguishable from the control (placebo) group.

Grimsgaard examined the effect of 3.8g/day of EPA versus 3.6g/day of DHA administered to people with normal triglyceride levels for 7 weeks.[2033] The results from the Grimsgaard study show that both DHA and EPA reduce triglycerides. The authors state that the net decrease in triglycerides was consistently greater for DHA. Grimsgaard also concludes that DHA may be responsible for the beneficial increase in HDL-C observed with some n-3 fatty acid supplements, which is consistent with previous studies which "suggested that serum HDL-C is better maintained with oil rich in DHA than oil rich in EPA."[2034] Although Grimsgaard states that EPA may produce a small decrease in serum total cholesterol, it does not specifically comment on EPA's effect on LDL-C.

Defendants completely misconstrue the results of Grimsgaard. Defendants attempt to characterize a non-significant increase in LDL-C by DHA and a non-significant decrease in

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[2032] Defendants' Joint Invalidity Contentions at 532.

[2033] Defendants state in their Joint Invalidity Contentions at 211 that Grimsgaard was conducted in patients with TG levels in the borderline-high/high ranges. This is incorrect; Grimsgaard was conducted in patients with normal TG levels. (*See* Grimsgaard at Abstract (describing participants as "healthy") and Table 4).

[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) | | | Contrasts between groups: $P$ | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Change | Baseline | Change | Baseline | Change | $F$ test: $P$[1] | DHA vs EPA | DHA vs corn oil | EPA vs corn oil |
| Triacylglycerols (mmol/L) | 1.24 ± 0.58[2] | −0.22 ± 0.31[3] | 1.23 ± 0.57 | −0.15 ± 0.40[4] | 1.22 ± 0.55 | 0.11 ± 0.34[4] | 0.0001 | 0.14 | 0.0001 | 0.0001 |
| Total cholesterol (mmol/L) | 6.00 ± 0.95 | 0.03 ± 0.49 | 5.98 ± 0.94 | −0.15 ± 0.55[5] | 6.02 ± 1.08 | 0.10 ± 0.55 | 0.01 | 0.04 | 0.4 | 0.004 |
| LDL cholesterol (mmol/L) | 4.06 ± 0.86 | 0.07 ± 0.46 | 4.06 ± 0.83 | −0.08 ± 0.48 | 4.04 ± 0.98 | 0.06 ± 0.48 | 0.10 | — | — | — |
| HDL cholesterol (mmol/L) | 1.36 ± 0.30 | 0.06 ± 0.13[3] | 1.33 ± 0.31 | 0.01 ± 0.12 | 1.41 ± 0.28 | −0.01 ± 0.11 | 0.001 | 0.009 | 0.0005 | 0.4 |
| Apolipoprotein A-I (g/L) | 1.38 ± 0.21 | 0.02 ± 0.13 | 1.38 ± 0.20 | −0.04 ± 0.10[5] | 1.46 ± 0.23 | 0.00 ± 0.12 | 0.003 | 0.0008 | 0.3 | 0.02 |
| Apolipoprotein B (g/L) | 1.00 ± 0.21 | −0.01 ± 0.11 | 1.01 ± 0.23 | −0.03 ± 0.11[5] | 1.02 ± 0.28 | 0.02 ± 0.11 | 0.05 | — | — | — |
| HDL:apolipoprotein A-I | 0.97 ± 0.14 | 0.04 ± 0.07[3] | 0.96 ± 0.13 | 0.04 ± 0.08[5] | 0.97 ± 0.12 | −0.01 ± 0.06 | 0.0001 | 0.8 | 0.0003 | 0.0001 |
| Total:HDL cholesterol | 4.62 ± 1.19 | −0.19 ± 0.52[4] | 4.70 ± 1.24 | −0.13 ± 0.47[5] | 4.43 ± 1.19 | 0.11 ± 0.62 | 0.002 | 0.4 | 0.0006 | 0.007 |

[1] ANOVA for between-group comparisons of change.
[2] $\bar{x}$ ± SD.
[3–5] One-sample $t$ test of difference between baseline and 7 wk: [3] $P < 0.001$, [4] $P < 0.01$, [5] $P < 0.05$.

Grimsgaard concludes that both DHA and EPA lower TG levels but have "differential effects on lipoprotein and fatty acid metabolism."[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.

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."[2037] Grimsgaard makes no such statement regarding LDL-C.

Defendants cherry-pick results, regardless of whether the effect is found to be statistically significant compared to placebo, in an attempt to force the studies to support their argument that it was well known to one of ordinary skill in the art that DHA increases LDL-C while EPA did not. This illustrates the hindsight reasoning driving Defendants' analysis of the prior art and proposed combinations of prior art. Defendants point to a non-significant increase in DHA and non-significant decrease in EPA in Grimsgaard as confirmation "that administration of purified DHA results in increased LDL-C levels while administration of purified EPA resulted in a decrease in LDL-C levels." The results from Grimsgaard clearly show that EPA and DHA did not have statistically significantly effects on LDL-C compared to placebo.[2038] A person of ordinary skill would not draw conclusions regarding differences between EPA and DHA based on statistically insignificant results.

Defendants also rely on Takaku to support their assertion that "clinical benefits of administering purified EPA—lowering triglycerides without raising LDL-C" was known in the

[2037] Grimsgaard at 654.

[2038] In Mori 2000, EPA resulted in a non-significant 0.18 mmol/L increase in LDL-C, while DHA caused a statistically significant 0.37 mmol/L increase in LDL-C compared to placebo. Applying the same logic used to interpret Grimsgaard, that non-significant effects are nonetheless confirmation of an effect, Defendants should have argued that Mori 2000 was confirmation that both EPA and DHA increases LDL-C. However, they do not make such arguments for the obvious reason that it does not support their argument that EPA was known to have little or no impact on LDL-C levels.

art.[2039] Similar to Katayama and Matsuzawa, Takaku was conducted to test the efficacy and safety of Epadel (of undisclosed purity)[2040] based on long-term administration.[2041]

A person of ordinary skill would not have concluded based on Takaku that EPA lowers triglycerides without raising LDL-C, because of its unreliable study method. Takaku candidly acknowledges that "only a few subjects were examined" and cautions against drawing a conclusion "only from the results of the present study."[2042] Because the study did not include any placebo control, a person of ordinary skill in the art would understand these reports do not provide the ability to conclude that the observed lipid effects would have occurred independent of the drug that is administered. In addition, the study was conducted exclusively in Japanese patients, and a person of ordinary skill would not have expected the results to be applicable to the general population.[2043]

The mean baseline triglyceride level of the patients in Takaku was 245 mg/dL, and a person of ordinary skill would not have expected the results to be applicable to patients with triglycerides above 500 mg/dL. Takaku also excluded 6 subjects from the LDL-C study because measurement was not feasible due to "insufficient sample."[2044] It is possible that patients with triglycerides above 500 mg/dL were among those excluded because of the challenges involved in

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[2039] Defendants' Joint Invalidity Contentions at 529.

[2040] It is possible that the version of Epadel used in the Katayama study fails to meet the purity limitation required by the claims. *See* Nishikawa (91% E-EPA preparation), Ando at 2177 (Epadel with purity greater than 91%), Nakamura at 23 (Epadel with purity > 90%).

[2041] Takaku at ICOSAPENT_DFNDT00006834.

[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.

calculating LDL-C levels when triglyceride level is above 400 mg/dL.[2045] Moreover, the study does not provide different LDL-C graphs based on the baseline triglyceride levels.[2046] Therefore, it is impossible to determine whether the patients with triglycerides above 500 mg/dL had increased or decreased LDL-C after taking MND-21. In addition, the graph of the rate of LDL-C change in patients with normal baseline LDL-C shows that the LDL-C change was volatile throughout the study period, decreasing slightly at times but increasing by more than 8% at other times.[2047] Because of this volatility, a person of ordinary skill would not be able to conclude what effect EPA has on LDL-C. Indeed, Takaku did not conclude that there was no increase in LDL-C, stating only that the fluctuation in LDL-C was not significant.[2048]

A person of ordinary skill would not have concluded, based on Takaku, that purified EPA had any advantage over fish oil in its effect on LDL-C. Takaku states that a previous study has "confirmed a decrease in serum VLDL-cholesterol and serum LDL-cholesterol through the administration of *fish oil* to hypercholesterolemia patients."[2049] In contrast, Takaku states merely that the fluctuation in LDL-C was not significant in its study. Therefore, a person of ordinary skill would have concluded based on Takaku that any favorable LDL-C effect seen in the study was attributable to fish oil in general, not EPA specifically.

Therefore, Grimsgaard, Katayama, Matsuzawa and/or Takaku fail to substantiate Defendants' assertion that pure EPA lowers triglycerides without raising LDL-C. Further, other

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[2045] *See* Matsuzawa at ICOSPENT_DFNDTS00006450.

[2046] Takaku at Fig. 13, ICOSAPENT_DFNDT00006882.

[2047] Takaku at Fig. 14, ICOSAPENT_DFNDT00006883.

[2048] Takaku at ICOSAPENT_DFNDT00006897.

[2049] Takaku at ICOSAPENT_DFNDT00006897.

studies cited by Defendants suggest that EPA increases LDL-C.[2050] Defendants identify no other basis upon which a person of ordinary skill would have sought to combine the Omacor PDR/Lovaza PDR with Katayama, Matsuzawa, Takaku, Grimsgaard, Mori 2000 and/or Maki.

(ii) Nozaki and/or Hayashi Would Not Have Rendered the Asserted Claims Obvious

Defendants contend that the asserted claims of the '399 patent would have been obvious in view Nozaki and/or Hayashi in combination with other references, but they do not explain why Nozaki and/or Hayashi render the asserted claims obvious or what element of the asserted claims is found in Nozaki or Hayashi. Nozaki and Hayashi do not disclose or suggest a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Nozaki administered 2.7 g/day of 90% EPA (DHA < 1%) to 14 primary hypercholesterolemia subjects. A person of ordinary skill would not have found the results of Nozaki reliable. Nozaki was not placebo-controlled, nor did the study compare lipid effect of EPA to that of DHA. The average baseline TG level was only 165 mg/dL, while the baseline LDL-C level was 185 mg/dL, which is unusually high for this TG patient population. A person of skill in the art would not look to a study consisting of patients with baseline TG levels of 165 mg/dL in order to understand the impact of EPA therapy on the very high TG patient population. Further, a person of ordinary skill would understand that the baseline LDL-C level in this small patient population were abnormally high and would not have relied upon these results. Further, the person of skill in the art would not have looked to this patient population to predict the Apo-

[2050] *See, e.g.*, Rambjor.

B or LDL-C effect of EPA therapy on very high TG patients. Nozaki acknowledges that as of 1991, "[t]here is still controversy concerning the effects of fish oil" on LDL and HDL cholesterol levels.[2051] Nozaki does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

In Hayashi, 1.8 g/day of EPA was administered to 28 patients for 8 weeks. The purity of the EPA and the DHA content in the composition that was administered is unknown. A person of ordinary skill would not have found the results of Hayashi reliable. The study involved 28 patients and it was conducted for only 8 weeks. Hayashi shows that changes in Apo-B and LDL-C were not statistically significant.[2052] Further, the person of skill in the art would not have looked to this patient population to predict the Apo-B or LDL-C effect of EPA therapy on very high TG patients. Hayashi does not provide a motivation or reasonable expectation of success for administering 4 grams of a pharmaceutical composition comprising at least about 96% EPA and substantially no DHA to patients with TG levels between 500 mg/dL to about 1500 mg/dL, to effect a reduction in trigylcerides without increasing LDL-C when purified EPA is administered to the very high TG patient population.

Further, Hayashi was a small study conducted in only Japanese patients and was not placebo controlled. This study would not have been extrapolated to Western populations because the Japanese diet contains much more fish and has a number of other different attributes.

[2051] Nozaki at 256.

[2052] Hayashi at 26, Table I.