UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

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AMARIN PHARMA, INC., *et al.*, Plaintiffs, v. HIKMA PHARMACEUTICALS USA INC., *et al.*, Defendants.	Case No. 2:16-cv-02525-MMD-NJK BENCH ORDER

I. SUMMARY

This is a consolidated patent infringement case brought under the Hatch-Waxman Act where Plaintiffs Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited (collectively, "Amarin") seek to prevent Defendants West-Ward Pharmaceuticals International Limited and Hikma Pharmaceuticals USA Inc. (collectively, "Hikma"), and Dr. Reddy's Laboratories, Inc. and Dr. Reddy's Laboratories, Ltd. (collectively, "DRL") from launching generic competitor drugs to Plaintiffs' drug Vascepa®. This order follows a bench trial the Court held in January 2020 (the "Trial"). As further explained below in the Court's findings of fact and conclusions of law, the Court finds that Defendants infringe the asserted claims under Plaintiffs' inducement theory, but the asserted patent claims are all invalid as obvious.

II. CLAIMS

Plaintiffs sued Defendants under the patent laws of the United States, 35 U.S.C. § 100, *et seq.*, including 35 U.S.C. § 271(e)(2), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202, arising from Defendants' filing of Abbreviated New Drug Applications ("ANDAs") under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA"),

21 U.S.C. § 355(j), seeking approval from the United States Food and Drug Administration ("FDA") to market generic versions of Plaintiffs' Vascepa product. (ECF No. 324 at 2.)

Plaintiffs specifically assert infringement of U.S. Patent No. 8,293,728 ("the '728 patent"), U.S. Patent No. 8,318,715 ("the '715 patent"), U.S. Patent No. 8,357,677 ("the '677 patent"), U.S. Patent No. 8,367,652 ("the '652 patent"), U.S. Patent No. 8,431,560 ("the '560 patent"), and U.S. Patent No. 8,518,929 ("the '929 patent").[1] (ECF No. 331 at 9.) Each of the Asserted Patents is entitled "METHODS OF TREATING HYPERTRIGLYCERIDEMIA." (*Id.*) The U.S. applications that ultimately issued as the Asserted Patents are continuations of U.S. Application No. 12/702,889, filed on February 9, 2010, which ultimately issued as the U.S. Patent No. 8,293,727 ("the '727 patent"). (*Id.*) The Asserted Patents further claim priority to U.S. Provisional Application No. 61/151,291, filed on February 10, 2009, and U.S. Provisional Application No. 61/173,755, filed on April 29, 2009. (*Id.*)

Plaintiffs more specifically assert that Defendants infringe the following ten claims of the Asserted Patents: Claims 1 and 16 of the '728 patent, Claim 14 of the '715 patent, Claims 1 and 8 of the '677 patent, Claim 1 of the '652 patent, Claims 4 and 17 of the '560 patent, and Claims 1 and 5 of the '929 patent.[2] (ECF Nos. 331 at 9-10, 333 at 13 n.1.) Defendants asserted counterclaims of noninfringement and invalidity. (ECF Nos. 27 at 28-34, 33 at 33-56.)

III. FINDINGS OF FACT

The Court makes the following findings of fact based on the testimony and other evidence admitted during the course of the Trial, along with the pre-trial and post-trial briefing the parties filed in this case.

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[1]Collectively, the "Asserted Patents."

[2]Collectively, the "Asserted Claims."

A. Factual Background

The Asserted Patents are directed to methods of beneficially lowering the levels of certain fats in the bloodstream using drugs made of purified omega-3 fatty acids from fish oil. Fats are natural biological molecules that scientists call "lipids." Triglycerides ("TGs") and cholesterol are two types of lipids that are of major importance in human physiology. TGs are high in calories and are a major source of energy in the diet of humans. (ECF No. 370 at 1561:21-1562:21.) After they are absorbed from the intestine, triglycerides are broken down into their component molecules, resynthesized, and reassembled by the intestine into lipoproteins. Lipoproteins are spherical particles that travel through the bloodstream and contain lipids (such as triglycerides and cholesterol) as well as proteins. (ECF Nos. 366 at 324:5-9, 370 at 1562:12-17.) The major proteins that are in lipoproteins are called apolipoproteins. One type of apolipoprotein is Apo B.

Cholesterol levels measured in a clinical laboratory generally include levels of both free cholesterol and cholesteryl ester. (ECF No. 333 at 8.) The level of cholesterol measured in the blood is generally an indicator for the amount of low-density lipoprotein cholesterol ("LDL-C") in the blood. (*Id.*) LDL-C is the "bad" cholesterol that physicians try to reduce in their patients with drugs such as statins. (*Id.*) In many patients, there is a strong linear relationship between levels of LDL-C and Apo B. (*Id.*) In other words, changes in LDL-C levels occur in parallel with changes in Apo B, reflecting the fact that there is one molecule of Apo B per LDL particle. (*Id.*)

The Asserted Claims are directed to methods of treating severe hypertriglyceridemia, a condition in which a patient's fasting TG levels rise to very high levels of 500 mg/dL or above. (ECF No. 377 at 33.) The term "hypertriglyceridemia" ("HTG") refers to having elevated TGs, which are the most abundant type of fat in the blood. (ECF No. 373 at 27.) The clinical guidelines that both sides rely on in this case, called "ATP III," define "normal triglycerides" as less than 150 mg/dL, with levels above

that considered elevated to various degrees. (Ex. 1526[3] (National Institutes of Health, National Heart, Lung, and Blood Institute, "*Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), Executive Summary*," May 2001 ("ATP-III Executive Summary")) at 27.) These numbers are referring to the "concentrations of triglycerides in the blood, and [] are always taken in the fasting state." (ECF No. 366 at 329:4-17.)

Severe hypertriglyceridemia "has a well-known meaning to doctors who treat the condition." (*Id.* at 454:6-8.) It "means that a patient has had triglycerides levels greater than or equal to 500 milligrams per deciliter." (ECF No. 365 at 52:24-3; *see also* ECF No. 366 at 454:9-12.) In other words, "as long as the patients have [TG] levels above 500, regardless of why, they have severe hypertriglyceridemia." (ECF No. 366 at 455:8-11.) This definition is consistent with the ATP-III guidelines as well as the Vascepa indication. (Ex. 1526 at 27; Ex. 2248 at 1.)

For most patients with elevated TGs, "the primary aim of therapy is to achieve the target goal for LDL[-C levels]." (Ex. 1526 at 27.) This is because research has long shown that "elevated LDL cholesterol is a major cause of CHD"—*i.e.*, coronary heart disease. (*Id.* at 11.)

The primary aim of therapy is different in patients with severe HTG because they have an elevated risk of acute pancreatitis. Pancreatitis, which involves the inflammation of the pancreas, is an excruciatingly painful and potentially life-threatening condition. (ECF No. 370 at 1567:2-22 ("In the setting of severe hypertriglyceridemia, inflammatory changes [c]an occur within the pancreas that can lead to sudden devastating injury to the pancreas leading to dissolution of pancreatic tissue, resulting in severe pain, inability to eat, to drink, and it constitutes a medical emergency. But even more importantly[,] in some cases[,] it [can] even result in death."); *see also* ECF Nos. 366 at 331:3-20, 365 at 72:4-13.) In

[3]The designation "Ex." refers to exhibits published by the parties during Trial and admitted by the Court. They are not filed on the docket but are available for public review in the Clerk of Court's office at 400 S. Virginia St. in Reno, Nevada, upon request, by referencing the case number of this case.

patients with severe hypertriglyceridemia, the primary "aim of therapy is to prevent acute pancreatitis through triglyceride lowering." (ECF No. 366 at 457:11-15; *see also* Ex. 1526 at 19.) This is the "primary treatment aim [in patients with severe hypertriglyceridemia] regardless of why the patient has triglycerides above 500." (ECF No. 366 at 457:16-18.) This is because "pancreatitis can be a life-threatening condition." (*Id.* at 473:18-20; *see also id.* at 568:10-16.)

As noted, the Asserted Claims are directed to methods of treating severe HTG specifically by administering 4 grams ("4 g") per day of purified EPA. Treating patients with severe hypertriglyceridemia with purified EPA reduced TGs in those patients without increasing LDL-C, the bad-cholesterol. (ECF Nos. 367 at 851:15-852:1, 370 at 1574:3-1575:1, 1598:14-17.) Other treatments for severe hypertriglyceridemia dramatically increase LDL-C levels, which then often requires the administration of a separate concurrent cholesterol-lowering drug, such as a statin, just to address that LDL-C increase. (ECF Nos. 367 at 813:8-814:2, 370 at 1598:18-1599:18.) Additionally, purified EPA has now been shown to actually reduce cardiovascular risk in severely hypertriglyceridemic patients on top of a statin, the only TG-lowering treatment shown to confer such a benefit. (ECF Nos. 367 at 849:21-24, 368 at 1122:6-13, 370 at 1622:5-16, 1625:2-21.) Treating severe HTG with purified EPA therefore offers several benefits over other possible treatments.

B. Plaintiff's Drug

Vascepa is a highly purified preparation of EPA (eicosapentaenoic acid), also known as icosapent ethyl. (ECF No. 324 at 24.) FDA first approved Vascepa in July 2012 as "an adjunct to diet to reduce triglyceride ("TG") levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." (*Id.*) Amarin currently markets Vascepa in both 1 g and 500 mg capsules. (Ex. 1186 at 2.) The daily dose of Vascepa is 4 grams per day, taken as two 1-gram (or four 500 mg) capsules twice daily with food. (ECF No. 324 at 24.)

Vascepa embodies the Asserted Claims. Vascepa contains a "pharmaceutical composition," as required by Claims 1 and 16 of the '728 patent, Claim 14 of the '715

patent, Claims 1 and 8 of the '677 patent, Claim 1 of the '652 patent, and Claims 1 and 5 of the '929 patent. The "pharmaceutical composition" in Vascepa comprises "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters," as required by Claims 1 and 16 of the '728 patent, Claims 1 and 8 of the '677 patent, and Claims 1 and 8 of the '652 patent. Vascepa further contains a "pharmaceutical composition" "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," as required by Claim 16 of the '728 patent. (*Id.* at 25.) The "pharmaceutical composition" in Vascepa also comprises "at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (["]DHA["]) or its esters," as required by Claim 14 of the '715 patent. (*Id.*) Vascepa comprises a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present," as required by Claims 4 and 17 of the '560 patent. (*Id.*) Finally, the "pharmaceutical composition" in a daily dose of Vascepa comprises "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids," as required by Claims 1 and 5 of the '929 patent. (*Id.*)

C. Defendants' ANDA Applications and Products

In 2016, after Vascepa's initial period of exclusivity against generic competition expired, Defendants filed ANDAs seeking FDA approval to market generic versions of Vascepa. As required by law, Defendants' ANDAs adopted the "same" labelling as Vascepa, which at the time was only approved for severe hypertriglyceridemia. *See* 21 U.S.C. §§ 355(j)(2)(A)(v), (j)(4)(G). However, Plaintiffs have since won FDA approval of a second indication for Vascepa—reducing the risk of adverse cardiovascular events. Now that Vascepa has two indications, the law "permits [Defendants] to file ANDAs directed to a subset of FDA-approved indications and even provides a mechanism for [Defendants] to affirmatively carve out" the new indication from their labels. *AstraZeneca Pharm. LP v. Apotex Corp*., 669 F.3d 1370, 1381 (Fed. Cir. 2012). Thus, Defendants' current labels do

not include Vascepa's new indication, and are materially the same as the labels the Court previously considered in ruling on the parties' summary judgment motions.

1. Hikma's ANDA

On or about July 26, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc., through Roxane Laboratories, Inc. (incorporated in Nevada), submitted to FDA an ANDA (ANDA No. 209457) with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of Vascepa® (icosapent ethyl) 1 g capsules as Icosapent Ethyl Capsules, 1 gram ("Hikma's ANDA Product"). (ECF No. 24 at 22.)

Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated September 21, 2016, Hikma Pharmaceuticals PLC and Roxane Laboratories, Inc. notified Amarin that they had submitted to FDA ANDA No. 209457, with paragraph IV certifications for the Asserted Patents. (*Id.*)

On or about December 8, 2016, Roxane Laboratories, Inc. transferred ANDA No. 209457 to West-Ward Pharmaceuticals International Limited. (*Id.*)

On or about December 8, 2016, West-Ward Pharmaceuticals International Limited appointed West-Ward Pharmaceuticals Corp. as its agent for purposes of communication with FDA regarding ANDA No. 209457. (*Id.* at 23.)

West-Ward Pharmaceuticals International Limited has changed its name to Hikma Pharmaceuticals International Limited. (*Id.*)

On or about July 8, 2019, Hikma Pharmaceuticals International Limited transferred ANDA No. 209457 to Hikma Pharmaceuticals USA Inc. Hikma Pharmaceuticals USA Inc. is now the owner of ANDA No. 209457. (*Id.*)

Vascepa is the Reference Listed Drug ("RLD") for ANDA No. 209457. (ECF No. 324 at 25.) Hikma's ANDA Product, if approved, will be bioequivalent to Vascepa. (*Id.*) The indication set forth in the proposed labeling for Hikma's ANDA Product, submitted in connection with ANDA No. 209457, is "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia." (*Id.* at 26.) The

dosage form of Hikma's ANDA Product, if approved, will be a 1- gram soft-gelatin capsule. (*Id.*) The daily dose of Hikma's ANDA Product, if approved, will be 4 grams per day taken as two 1-gram capsules twice daily with food. (*Id.*) Hikma's ANDA Product, if approved, will contain icosapent ethyl. (*Id.*)

Hikma's ANDA Product, if approved, will contain a "pharmaceutical composition," as required by Claims 1 and 16 of the '728 patent, Claim 14 of the '715 patent, Claims 1 and 8 of the '677 patent, Claim 1 of the '652 patent, and Claims 1 and 5 of the '929 patent. (*Id.*) The "pharmaceutical composition" in Hikma's ANDA Product, if approved, will comprise "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters," as required by Claims 1 and 16 of the '728 patent, Claims 1 and 8 of the '677 patent, and Claim 1 of the '652 patent. (*Id.*) Hikma's ANDA Product, if approved, will contain a "pharmaceutical composition" "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," as required by Claim 16 of the '728 patent. (*Id.*) Hikma's ANDA Product, if approved, will comprise a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present," as required by Claims 4 and 17 of the '560 patent. (*Id.* at 26-27.) The "pharmaceutical composition" in a daily dose of Hikma's ANDA Product, if approved, will comprise "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids," as required by Claims 1 and 5 of the '929 patent. (*Id.* at 27.)

2. DRL's ANDA

On or about July 26, 2016, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA an ANDA (ANDA No. 209499) with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), seeking approval to market a generic version of Vascepa (icosapent ethyl) 1 g capsules as Icosapent Ethyl Capsules, 1 gram ("DRL's ANDA Product"). (*Id*. at 23)

Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated September 22, 2016, DRL notified Amarin that it had submitted to FDA ANDA No. 209499, with paragraph IV certifications for the Asserted Patents. (*Id.* at 24.)

On or about July 11, 2018, DRL, through Dr. Reddy's Laboratories, Inc., submitted to FDA a supplement to ANDA No. 209499 with paragraph IV certifications under Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for 500 mg icosapent ethyl capsules purportedly bioequivalent to Vascepa. (*Id.*)

Pursuant to 21 U.S.C. § 355(j)(2)(B), in a letter dated July 11, 2018, DRL notified Amarin that it had submitted to FDA a supplement to ANDA No. 20499, with paragraph IV certifications for the '728, '715, '677, '652, and '929 patents. (*Id.* at 24.)

Vascepa is the RLD for ANDA No. 209499. DRL's ANDA Product, if approved, will be bioequivalent to Vascepa. (*Id.* at 27.) The indication set forth in the proposed labeling for DRL's ANDA Product, submitted in connection with ANDA No. 209499, is "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." (*Id.*) The dosage form of DRL's ANDA Product, if approved, will be a 1-gram soft-gelatin capsule. (*Id.*) The daily dose of DRL's ANDA Product, if approved, will be 4 grams per day taken as two 1-gram capsules twice daily with food. DRL's ANDA Product, if approved, will contain icosapent ethyl. (*Id.*)

DRL's ANDA Product, if approved, will contain a "pharmaceutical composition," as required by Claims 1 and 16 of the '728 patent, Claim 14 of the '715 patent, Claims 1 and 8 of the '677 patent, Claim 1 of the '652 patent, and Claims 1 and 5 of the '929 patent. (*Id.*) The "pharmaceutical composition" in DRL's ANDA Product, if approved, will comprise "at least about 96%, by weight of all fatty acids present, ethyl eicosapentaenoate[,] and substantially no docosahexaenoic acid or its esters," as required by Claims 1 and 16 of the '728 patent, Claims 1 and 8 of the '677 patent, and Claim 1 of the '652 patent. (*Id.*)

DRL's ANDA Product, if approved, will contain a "pharmaceutical composition" "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," as required by Claim 16 of

the '728 patent. (*Id.* at 27-28.) The "pharmaceutical composition" in DRL's ANDA Product, if approved, will comprise "at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters," as required by Claim 14 of the '715 patent. (*Id.* at 28.) DRL's ANDA Product, if approved, will comprise a capsule comprising 950 mg to 1050 mg of ethyl eicosapentaenoate. DRL did not assert the claim limitation from Claims 4 and 17 of the '560 patent that recites a "capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate" as a basis for noninfringement of Claims 4 and 17 of the '560 patent. (*Id.*) DRL's ANDA Product, if approved, will comprise "a capsule comprising . . . not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present," as required by Claims 4 and 17 of the '560 patent. (*Id.*) The "pharmaceutical composition" in a daily dose of DRL's ANDA Product, if approved, will comprise "about 4 g of ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids," as required by Claims 1 and 5 of the '929 patent. (*Id.*)

D. The Asserted Patents

1. The '728 Patent

The '728 patent issued on October 23, 2012 to Mehar Manku, Ian Osterloh, Pierre Wicker, Rene Braeekman, and Paresh Soni (collectively, "Inventors"). The patent issued from Application No. 13/349,153 ("the '153 application"). (ECF No. 324 at 4.)

Claims 1 and 16 of the '728 patent are asserted. The asserted claims of the '728 patent, and any claims from which they depend, are reproduced below.

> 1. A method of reducing triglycerides in 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 comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight of all fatty acids present, ethyl eicosapentaenoate, and substantially no docosahexaenoic acid or its esters for a period of 12 weeks 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.

> 16. The method of claim 1, 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.

2. The ’715 Patent

The ’715 patent issued on November 27, 2012 to the Inventors. The patent issued from Application No. 13/282,145 (“the ’145 application”). (ECF No. 324 at 4.) Claim 14 of the ’715 patent is asserted. The asserted claims of the ’715 patent, and any claims from which they depend, are reproduced below.

> 13. A method of reducing triglycerides in 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, comprising administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight, ethyl eicosapentaenoate (ethyl-EPA) and substantially no docosahexaenoic acid (DHA) or its esters for a period of at least 12 weeks to effect a statistically significant reduction in triglycerides without effecting a statistically significant increase in LDLC or apolipoprotein B in the subject.
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> 14. The method of claim 13 comprising administering to the subject about 4 g per day of the pharmaceutical composition to effect a statistically significant reduction in triglycerides and apolipoprotein B without effecting a statistically significant increase of LDL-C in the subject.

3. The ’677 Patent

The ’677 patent issued on January 22, 2013, to the Inventors. The patent issued from Application No. 13/608,775 (“the ’775 application”). (ECF No. 324 at 4.) Claims 1 and 8 of the ’677 patent are asserted. The asserted claims of the ’677 patent, and any claims from which they depend, are reproduced below.

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of at least about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to placebo control.
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> 8. The method of claim 1, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of at least about 12 weeks to effect a reduction in apolipoprotein B compared to placebo control.

4. The ’652 Patent

The ’652 patent issued on February 5, 2013 to the Inventors. The patent issued from Application No. 13/610,247 (“the ’247 application”). (ECF No. 324 at 5.) Claim 1 of the ’652 patent is asserted. The asserted claim of the ’652 patent is reproduced below.

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising: administering orally to the subject about 4 g per day of a pharmaceutical composition comprising at least about 96% by weight of all fatty acids present, ethyl eicosapentaenoate and substantially no docosahexaenoic acid or its esters for a period of about 12 weeks to effect a reduction in triglycerides without substantially increasing LDL-C compared to baseline.

5. The ’560 Patent

The ’560 patent issued on October 23, 2012 to the Inventors. The patent issued from Application No. 13/711,329 (“the ’329 application”). (ECF No. 324 at 5.) Claims 4 and 17 of the ’560 patent are asserted. The asserted claims of the ’560 patent, and any claims from which they depend, are reproduced below.

> 1. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject.
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> 4. The method of claim 1, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing the LDL-C by more than 5% in the subject.
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> 11. A method of reducing triglycerides in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl comprising, administering orally to the subject 4 capsules per day, each capsule comprising about 900 mg to about 1 g of ethyl eicosapentaenoate and not more than about 3% docosahexaenoic acid or its esters, by weight of total fatty acids present, for a period of 12 weeks to effect a reduction in triglycerides in the subject compared to placebo control.
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> 17. The method of claim 11, wherein said administering effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject compared to placebo control.

6. The ’929 Patent

The ’929 patent issued on August 27, 2013 to the Inventors. The patent issued from Application No. 13/776,242 (“the ’242 application”). (ECF No. 324 at 5.) Claims 1 and 5 of

the '929 patent are asserted. The asserted claims of the '929 patent, and any claims from which they depend, are reproduced below.

> 1. A method of reducing triglycerides in a subject having fasting triglycerides of at least 500 mg/dl comprising, orally administering to the subject daily for at least about 12 weeks a pharmaceutical composition comprising about 4 g ethyl eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.
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> 5. The method of claim 1, wherein 12 weeks of said daily administration is effective to reduce apolipoprotein B in subjects who have fasting triglycerides levels of at least 500 mg/dl.

Pursuant to 21 U.S.C. § 355(b)(1), the Asserted Patents are listed in the Orange Book—published by FDA and formally known as Approved Drug Products with Therapeutic Equivalence Evaluations—in connection with New Drug Application ("NDA") No. 202057. (ECF No. 324 at 4.) Because the Asserted Patents are related, their disclosures—the information contained within their respective specifications—are essentially the same. (ECF No. 377 at 65.) All of the Asserted Patents were initially rejected as obvious, but the patent examiner responsible for reviewing them later issued materially identical statements of allowance permitting the Asserted Patents to issue because he found that certain secondary considerations of nonobviousness made the Asserted Claims patentable. (*Id.* at 61-65.) He specifically found the pending claims patentable because "Applicant was able to overcome the above 103 obviousness rejection by showing: 1 - Unexpected results, and 2 - Long felt unmet medical need." (*See, e.g.*, Ex. 38 at 1831.)

E. Witnesses

Both Plaintiffs and Defendants had witnesses, mostly experts, who testified at the Trial. The parties also stipulated to the admission of the deposition testimony of other expert witnesses, and the Court admitted that testimony. The Court briefly describes the witnesses below.

1. Live Testimony

The following witnesses testified on Plaintiffs' behalf during the Trial. Matthew Budoff M.D. was admitted as an expert in the clinical treatment of patients with lipid

disorders, including severe hypertriglyceridemia, and as an expert in cardiology. (ECF No. 366 at 323:11-14.)[4] Dr. Budoff's testimony focused on the infringement portion of the case. Plaintiffs also had a fact witness testify—Steven Ketchum, Ph.D. Dr. Ketchum is the President of Research & Development, a Senior Vice President, and the Chief Scientific Officer at Amarin Pharma, Inc. (ECF No. 365 at 49:18-19.) Dr. Ketchum's testimony focused on the history of Amarin and the development of Vascepa. Plaintiffs also offered the expert testimony of Sean Nicholson, Ph.D. Dr. Nicholson was admitted as an expert in the economics of the pharmaceutical industry. (ECF No. 369 at 1421:6-11.) He testified about the commercial success of Vascepa and its nexus to the Asserted Claims. (*Id.* at 1417:13-1538:6.) Plaintiffs also offered Carl Peck M.D. as an expert in FDA regulation of new and generic drugs including prescription drug labeling. (*Id*. at 1323:16-23.) In addition, Peter Toth, M.D., Ph.D. was admitted as an expert in lipidology, the treatment of severe hypertriglyceridemia, including severe hypertriglyceridemia, and the prevention and treatment of cardiovascular disease. (ECF No. 370 at 1560:11-17.) Dr. Toth testified regarding the non-obviousness of the Asserted Patents, and about the clinical attributes of Vascepa. (*Id.* at 1546:9-1783:13.)

Defendants called expert witnesses Jonathan Sheinberg (non-infringement), Jay Heinecke (invalidity), Edward Fisher (invalidity), and Ivan Hofmann (rebutting commercial success). (ECF No. 373 at 19.) Dr. Sheinberg, a board-certified cardiologist, testified as Defendants' non-infringement expert. (*Id.* at 19-21.) Dr. Heinecke, an endocrinologist and expert in lipoprotein metabolism and lipid disorders, testified as one of Defendants' invalidity experts. (*Id.*) Dr. Fisher, a biochemist and expert in cardiovascular medicine, also testified as one of Defendants' invalidity experts. (*Id.*) Mr. Hofmann, an economist, testified as Defendants' commercial success expert. (*Id.*)

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[4]References to the Trial transcripts (ECF Nos. 365-371) are to the transcript page numbers, not the page numbers of that particular document in the CM/ECF system.

2. Deposition Testimony

As mentioned, the parties also stipulated to the admission of the following deposition testimony.

Jerald Andry, Pharm.D. (Defendant Hikma's Witness). Andry is the Senior Director of Drug Regulatory Affairs and Medical Affairs at Hikma Pharmaceuticals USA Inc. (Andry Dep. Tr. 8:15-23, 29:3-9.)[5]

Jaya Ayyagari (Defendant DRL's Witness). Ayyagari is the Director of Regulatory Affairs at Dr. Reddy's Laboratories, Inc. (Ayyagari Dep. Tr. 5:9-21, 27:25-28:5.)

Harold E. Bays, M.D. (Third-Party Witness). Dr. Bays is the Medical Director and President of Louisville Metabolic and Atherosclerosis Research Center. Dr. Bays submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

Andrea Cady, Ph.D. (Defendant Hikma's Witness). Cady is the Senior Director of Product Development at Hikma Pharmaceuticals USA Inc. (Cady Dep. Tr. 9:5-16.)

Philip Lavin, Ph.D. (Third-Party Witness). Dr. Lavin has a Ph.D. in Applied Mathematics from Brown University. Dr. Lavin is self-employed through Lavin Consulting LLC as a biostatistics consultant. Dr. Lavin submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents.

Mehar Manku, Ph.D. (Third-Party Witness). Dr. Manku is one of the named inventors of the Asserted Patents. While he no longer works there, throughout his career at Amarin, Dr. Manku played a central role in the development of Vascepa. (Manku Dep. Tr. 8:22-9:17, 10:5-12:11, 14:19-16:6, 31:10-32:12, 48:19-50:11.)

Peter R. Mathers (Defendants' Expert). Mathers is a partner in the Washington, D.C. law firm of Kleinfeld, Kaplan and Becker LLP, where he practices food and drug law.

[5]The designation "Dep. Tr." refers to deposition transcripts admitted as evidence by the Court on the parties' stipulation in lieu of reading them into the record at Trial. They are also available for public review in the Clerk of Court's office at 400 S. Virginia St. in Reno, Nevada.

Mathers was retained by Defendants to provide opinions regarding issues relating to patent infringement. (Mathers Dep. Tr. 11:13-24.)

Michael Miller, M.D. (Plaintiffs' Claim Construction Declarant). Dr. Miller is Professor of Cardiovascular Medicine, Epidemiology and Public Health at the University of Maryland School of Medicine. Plaintiffs asked Dr. Miller to offer his expert opinion during claim construction regarding how a person of ordinary skill in the art ("POSA") would understand certain terms in the Asserted Claims.

Ian Osterloh, M.D. (Third-Party Witness). Dr. Osterloh is one of the named inventors of the Asserted Patents. In 2007, Dr. Osterloh joined Amarin as a consultant on the severe hypertriglyceridemia clinical research and development program. (Osterloh Dep. Tr. 8:22-9:18, 22:24-23:24, 49:1-3.)

Anuj Srivastava, Ph.D. (Defendant DRL's Witness). At the time of his deposition, Dr. Srivastava was the Senior Director of Strategic Portfolio & Business Development at Dr. Reddy's Laboratories, Inc. (Srivastava Dep. Tr. 6:5-8, 17:15-18:15.)

Howard S. Weintraub, M.D. (Third-Party Witness). Dr. Weintraub submitted two declarations to the Patent and Trademark Office during prosecution of the Asserted Patents. (Weintraub Dep. Tr. 8:19-9:7, 10:2-16, 114:20-115:19, 185:9-11.)

F. Infringement

In general, prescription drug labels are referred to alternatively as the label, labeling, prescribing information, and/or package insert. (ECF No. 369 at 1324:13-18.) As discussed below, the Court finds that the Vascepa label supports Plaintiffs' view that clinicians generally prescribe Vascepa for long-term use of at least 12 weeks.

The Indications and Usage section of the Vascepa label states that "Vascepa (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." (Ex. 1186 at 2.)[6] The Indications

[6]The Indications and Usage section of Vascepa's current labeling adds a second approved indication: "as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and

and Usage section thus instructs clinicians that Vascepa is approved (*i.e.*, safe and effective) for use in combination with diet to reduce TGs in adult patients with severe hypertriglyceridemia—without concurrent administration of any other medication. (ECF No. 369 at 1352:12-20, 1375:16-19.)

The Indications and Usage section of the Vascepa label does not specify a duration of use. (Ex. 1186 at 2.) The absence of a limitation on duration tells clinicians that FDA has determined that there are no safety or efficacy concerns that require limiting the duration of use of Vascepa. (ECF No. 369 at 1373:1-11.) Given the lack of any duration of use combined with the indication to treat a chronic condition,[7] the Indications and Usage section instructs clinicians to prescribe VASCEPA long-term. (*Id.* at 1338:8-1339:6, 1373:19-1374:1.)

Prior to December 2019, Vascepa's labeling also included a "Limitation of Use" advising clinicians that Vascepa's effect on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia had not been determined. (*See* Ex. 940 at 2.) That "Limitation of Use" was dropped when FDA approved Vascepa's new indication for cardiovascular risk-reduction.[8] (*See* Ex. 1186 at 2.)

The Dosage and Administration section of the Vascepa label includes two sub-headings. The first reads, "2.1 Prior to Initiation of Vascepa." (*Id*.) Under this heading, the label advises clinicians to "[a]ssess lipid levels before initiating therapy. Identify other causes (*e.g.*, diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate." (*Id.*) This subheading also advises clinicians that "[p]atients should engage in appropriate nutritional intake and physical activity before receiving Vascepa, which should continue during treatment with Vascepa." (*Id.*)

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established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." (Ex. 1186 at 2.) This indication, referred to during the Trial as the "REDUCE-IT Indication" is carved out of Defendants' labels.

[7]In many cases, as discussed in more detail *infra* in the Court's conclusions of law.

[8]Again, the "REDUCE-IT Indication."

The second sub-heading is "2.2 Dosage and Administration." Here, the label states that "[t]he daily dose of Vascepa is 4 grams per day taken as either: four 0.5 gram capsules twice daily with food; or as two 1 gram capsules twice daily with food." (*Id.*) The label also instructs clinicians to "[a]dvise patients to swallow Vascepa capsules whole. Do not break open, crush, dissolve, or chew Vascepa." (*Id.*; *see also* ECF No. 365 at 68:24-69:16.)

The Dosage and Administration section in Vascepa's labeling does not specify a duration of use. (Ex. 1186 at 2.) The absence of a duration limitation in this section conveys that Vascepa's benefit does not stop after a particular duration of treatment. (ECF No. 369 at 1343:5-9.) This means that Vascepa was approved for long-term use to reduce TGs and maintain that reduction. (*Id.* at 1344:3-14.)

The Dosage and Administration section in Vascepa's labeling does not recommend use of any concomitant medication. (Ex. 1186 at 2.) This conveys that FDA approved Vascepa as a monotherapy to reduce TGs in adult patients with severe hypertriglyceridemia (ECF No. 369 at 1355:7-10), and that FDA does not believe that the safety or effectiveness of Vascepa depends on concurrent administration of another medication (*Id.* at 1354:20-25, 365 at 67:7-12).

The Dosage Forms and Strength section of the VASCEPA label informs clinicians that Vascepa is available as a 1-gram or 0.5-gram soft-gelatin capsule. (Ex. 1186 at 2; *see also* ECF No. 365 at 67:13-68:6.)

The Contraindications section of the Vascepa label states that Vascepa is contraindicated only in patients with known hypersensitivity to Vascepa or any of its components. (Ex. 1186 at 2.)

The Warnings and Precautions section of a drug label is intended to describe serious or otherwise clinically significant adverse reactions and safety hazards of which clinicians need to be aware before prescribing the drug. (ECF No. 366 at 358:10-15.) *See also* 21 C.F.R. § 201.57(c)(6). The Warnings and Precautions section of the Vascepa label states that Vascepa was associated with an increased risk of atrial fibrillation or atrial flutter and

an increased risk of bleeding. (Ex. 1186 at 2-3.) It also cautions against the use of Vascepa in patients with known hypersensitivity to fish and/or shellfish. (*Id.*)

Unlike Lovaza's[9] labeling, the Warnings and Precautions section of the Vascepa labeling does not warn of a potential increase in LDL-C levels. (ECF No. 366 at 407:7-25; *compare* Ex. 566 at 1 *with* Ex. 1186 at 2-3.)

The Description section of the Vascepa label informs clinicians that the active ingredient in Vascepa is "[i]cosapent ethyl," which "is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA)," and that "[e]ach VASCEPA capsule contains . . . 1 gram of icosapent ethyl (in a 1 gram capsule)." (Ex. 1186 at 6; *see also* ECF No. 365 at 68:7-23.) This section also states that Vascepa is for "oral use." (Ex. 1186 at 6; *see also* ECF No. 366 at 418:2-5.)

The Nonclinical Toxicology section of a prescription drug label discloses the results of studies conducted on rodents, or other non-human subjects. "It's generally expected that a carcinogenicity study be conducted in two rodent species to support marketing approval of a new chemical entity for a chronic use indication." (ECF No. 365 at 110:14-17.) Plaintiffs performed two such studies, and their results are reflected in the Nonclinical Toxicology section of the Vascepa label. (*Id.* at 111:11-20; *see also* Ex. 1186 at 8.) Both rodent studies, the rat study described in the first paragraph and the mouse study described in the second paragraph of the section, "supported there was no carcinogenic potential of icosapent ethyl." (ECF No. 365 at 112:11-7.)

The Clinical Studies section of the Vascepa label, sub-heading 14.2, describes the design and results of the MARINE study, the primary study that established Vascepa's effectiveness at reducing triglycerides in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. (Ex. 1186 at 10-11.)[10]

[9]A competing, older drug whose guide for use is prior art to the Asserted Claims. Lovaza is described in more detail *infra* in Section III.G.1(b).

[10]The 2019 label added to the Clinical Studies section the design and results of the REDUCE-IT study, under sub-heading 14.1. (Ex. 1186 at 8-10.) Like the rest of the

The Clinical Studies section, "14.2 Severe Hypertriglyceridemia," begins by summarizing the major design characteristics of the MARINE study. Section 14.2 states:

> The effects of Vascepa 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on Vascepa, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2,000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (76%). The mean age was 53 years and the mean body mass index was 31 kg/m^2. Twenty-five percent of patients were on concomitant statin therapy, 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL.

(Ex. 1186 at 10-11.)

Next, Section 14.2 of the Clinical Studies Section includes a table summarizing the "major lipoprotein lipid parameters for the groups receiving Vascepa or placebo" and beneath the table is a brief summary of the conclusions. (*Id.* at 11, Tbl. 2.)

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

Parameter	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9**(-14, -3)

% Change= Median Percent Change from Baseline
Difference= Median of [VASCEPA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
p-values from Wilcoxon rank-sum test
*p-value < 0.001 (primary efficacy endpoint)
**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

Beneath Table 2, there is a paragraph highlighting key results of the MARINE trial. (*Id.*)

REDUCE-IT Indication, this portion of the Clinical Studies section is carved out of Defendants' labels.

Amarin included the statements below Table 2 because it wanted to "apprise[]" "healthcare professionals" and "draw the healthcare professional's attention" to the "key information from that pivotal trial." (ECF No. 365 at 98:8-99:14.)

The Patient Counseling Information section of the Vascepa label instructs clinicians to "[a]dvise the patient to read the FDA-approved patient labeling before starting Vascepa (Patient Information)," and then lists five topics for discussion with patients: (1) the potential increased risk for atrial fibrillation or atrial flutter; (2) the potential for allergic reactions in patients with hypersensitivity to fish and/or shellfish; (3) the increased risk of bleeding, particularly in patients receiving other antithrombotic agents; (4) the need to swallow Vascepa capsules whole, and (5) and the need to take Vascepa as prescribed. (*See* Ex. 1186 at 11-12.)

The Patient Information page at the end of the label is a handout that patients may take with them. It reiterates much of the same information included in the label itself, but in lay language. (ECF No. 366 at 359:11-24; *see also* Mathers Dep. Tr. 126:2-5, 7-20 (explaining how the Patient Information page distills information into user-friendly language).)

Among other things, the Vascepa Patient Information sheet instructs patients to "[t]ake Vascepa exactly as your doctor tells you to take it" and to "not change your dose or stop taking Vascepa without talking to your doctor." (Ex. 1186 at 13-14.) The Patient Information sheet also instructs patients to "[t]ake VASCEPA capsules whole" and to "not break, crush, dissolve, or chew VASCEPA capsules before swallowing." (*Id.*) The Patient Information sheet also advises that "your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA." (*Id.*)

G. Obviousness

"Obviousness is a question of law based on underlying factual findings." *Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.,* 711 F.3d 1348, 1355 (Fed. Cir. 2013). The Court now discusses below its factual findings relevant to the question of

whether the Asserted Claims are obvious in view of the combinations of prior art advanced by Defendants.

1. Scope and Content of the Prior Art

The parties agree that the relevant prior art includes certain pieces of prior art. (ECF No. 324 at 6-16.) "[T]he scope of the relevant prior art … includ[es] that reasonably pertinent to the particular problem with which the inventor was involved. . . . A reference is reasonably pertinent if, even though it may be in a different field of endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re GPAC Inc.*, 57 F.3d 1573, 1577-78 (Fed. Cir. 1995) (quotation omitted). Amongst those references that the parties agree are prior art, the Court only discusses below the references that are relevant to its findings of law.

a) Priority Date

Plaintiffs proposed a priority date for all Asserted Patents of March 2008, based on emails sent by one of the Inventors (Manku (ECF Nos. 331 at 10, 377 at 174-76)) while Defendants proposed a priority date of February 2009, the filing date of the patents (ECF Nos. 333 at 55, 373 at 58-64). But the disputed priority date is not material, because Defendants argue all Asserted Claims would have been obvious as of Plaintiffs' alleged conception date in March 2008. (ECF No. 373 at 167 n. 14.) Further, both sides' experts assessed obviousness as of March 2008, and made clear that their opinions would not change if the priority date was February 2009. (ECF Nos. 367 at 827:8-10; 370 at 1638:5-10.) Thus, the Court assumes without deciding that the Asserted Patents are entitled to a priority date of March 2008, and its conclusions of law also address obviousness as of March 2008.

b) Lovaza PDR (2007)

The Lovaza PDR (Physician's Desk Reference) was published in 2007 and is prior art to the patents-in-suit.

Lovaza PDR discloses a commercially-available preparation of EPA and DHA administered at 4 grams/day, a pharmaceutical known as Lovaza. (Ex. 1535 at 2.) While the Lovaza PDR published in the 2008 version of the Physician's Desk Reference, Lovaza was first commercially launched in 2004. (ECF No. 367 at 745:10-21.) Lovaza PDR discloses that "Lovaza is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (> 500 mg/dl) triglyceride levels." (Ex. 1535 at 3.) As of the alleged priority date, Lovaza was "widely used" and "a very successful drug." (ECF No. 371 at 1891:7-12.)

Lovaza PDR discloses clinical trials in which Lovaza was administered as either "add-on therapy" to a statin or as "monotherapy." (Ex. 1535 at 2.) Under "High Triglycerides: Add-on to HMG-CoA reductase inhibitor therapy," the label explains:

> The effects of Lovaza 4 g per day as add-on therapy to treatment with simvastatin were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 254 adult patients (122 on Lovaza and 132 on placebo) with persistent high triglycerides (200-499 mg/dL) despite simvastatin therapy (Table 1).

(*Id.*)

In this study, Lovaza PDR explains that all patients were treated with "simvastatin 40 mg per day for 8 weeks prior to randomization to control their LDL-C." (*Id.*) After the addition of Lovaza 4 g per day to simvastatin 40 mg per day, the median change in LDL-C was an increase of 0.7% compared to baseline. (*Id.*) Relative to placebo, Lovaza 4 g per day further "significantly reduced" TG and Apo B levels. (*Id.*) A POSA reading Lovaza PDR would understand that "when Lovaza is used with simvastatin, Apo B is decreased by 4.2 percent" and "there's barely any LDL-C increase." (ECF No. 371 at 1872:19-24.) In fact, the combination of Lovaza and simvastatin essentially caused "zero" increase in LDL-C. (*Id.* at 1872:22-1873:2.)

Lovaza PDR also discloses data under "Very High Triglycerides: Monotherapy" in which "[t]he effects of Lovaza 4 g per day were assessed in two randomized, placebo-controlled, double-blind, parallel group studies of 84 adult patients (42 on Lovaza, 42 on placebo) with very high triglyceride levels (Table 2)." (Ex. 1535 at 2.) Table 2 summarizes data from "two studies of 6 and 16 weeks duration." (*Id.*) In the monotherapy study in

patients with very high triglycerides, treatment with Lovaza 4 g/day significantly reduced triglycerides but also caused a significant increase in LDL-C (an increase of 44.5% compared to baseline and 49.3% compared to placebo). (*Id.* at 3.)

Lovaza PDR therefore discloses "Lovaza treatment may result in elevations in LDL-C and non-HDL-C in some individuals." (*Id.*) However, as of March 2008, a skilled artisan "would understand that if a patient experiences LDL-C increases from Lovaza, [a] statin could be added to address that side effect." (ECF No. 371 at 1891:22-25.) A skilled artisan likewise knew that "Lovaza could be safely administered with statins" and was "typically well-tolerated." (*Id.* at 1874:22-24, 1893:9-11; *see also* ECF No. 367 810:11-14.) In fact, Lovaza's "rise in LDL-C was often offset by concurrent treatment with statins. The safety and efficacy of using prescription Omega-3 in combination with a statin has been well-established." (Ex. 1953 at 233; *see also* ECF Nos. 371 at 1875:2-16, 367 at 809:21-810:10.)

c) Mori (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. Clinical Nutrition 1085- 94 (2000) ("Mori") was published in 2000 and is prior art to the patents-in-suit.

Mori discloses "a double-blind, placebo-controlled trial of parallel design, [where] 59 overweight, nonsmoking, mildly hyperlipidemic men were randomly assigned to receive 4 g purified EPA, DHA, or olive oil (placebo) daily while continuing their usual diets for 6 wk." (Ex. 1538 at 1-2.) The objective of Mori was "to determine whether eicosapentaenoic (EPA) and docosahexaenic (DHA) acids have differential effects on serum lipids and lipoporoteins." (*Id.* at 1.)

Mori discloses that among the three treatment arms, "[c]apsules contained either purified preparations of EPA ethyl ester (~96%), DHA ethyl ester (~92%), or olive oil (~75% oleic acid ethyl ester)." (*Id.* at 2.) Further, "[n]one of the subjects were regularly taking nonsteroidal antiinflammatory, antihypertensive, or lipid-lowering drugs or other drugs

known to affect lipid metabolism." (*Id.* at 3.) Therefore, none of the patients in Mori were on concurrent lipid-altering therapy. (ECF No. 367 at 739:22-25.)

Mori reports that triacylglycerols (TGs) "decreased significantly by 18.4% with EPA (P = 0.012) and by 20% with DHA (P = 0.003)." (Ex. 1538 at 3.) A POSA would consider this difference in triglyceride reduction "indistinguishable and of no clinical significance." (ECF No. 367 at 740:1-13.) A POSA would likewise recognize that Mori teaches that "4 grams pure EPA could reduce triglycerides by about 20 percent." (ECF No. 371 at 1826:24-1827:5.)

Mori also reports that "[s]erum LDL cholesterol increased significantly with DHA (by 8%; P = 0.019), but not with EPA (by 3.5%; NS)," (Ex. 1538 at 3), "strongly suggesting that these two Omega-3 fatty acids could have distinct effects on LDL cholesterol levels" (ECF No. 367 at 740:1-17). In the Abstract, Mori summarizes these results as showing that while "LDL, HDL, and HDL2 cholesterol were not affected significantly by EPA, . . . DHA increased LDL cholesterol by 8% (P = 0.019)." (Ex. 1538 at 1; *see also* ECF No. 371 at 1827:8-11.) Mori concludes that "EPA and DHA had differential effects on lipids." (Ex. 1538 at 1; *see also* ECF No. 371 at 1827:8-19.) Therefore, "a skilled artisan would understand from Mori that DHA and EPA work differently." (ECF No. 371 at 1829:6-8.)

d) Hayashi (1995)

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") was published in 1995, and is prior art to the patents-in-suit.

Hayashi reports the daily administration of 1.8 grams per day of purified EPA over a period of eight weeks to patients with a serum triglyceride level above 150 mg/dl. (Ex. 1532 at 4.)

Hayashi investigated the effects of EPA in patients with "familial combined hyperlipidemia (["]FCH["]) showing phenotype IIa, IIb, or IV." (*Id.*) While Hayashi defined all three phenotypes as "FCH," (*id.*), a POSA would have understood that phenotype IV refers to the Fredrickson system of classifying lipid disorders. (ECF No. 371 at 1866:10-

12.) Fredrickson Type IV is not limited to patients with triglycerides > 500 mg/dL. (*See, e.g.*, Ex. 2005 at 6 (reporting a Zocor study in which patients with Fredrickson Type IV had a median triglyceride level of 404 mg/dL).) However, this phenotype includes patients with severe hypertriglyceridemia. (*See, e.g.*, Ex. 1986 at 21 (reporting a Lipitor study with a median baseline triglyceride level of 565 mg/dL in patients with Fredrickson Type IV); Ex. 3007 at 11-12; Ex. 939 at 5 (reporting a Lovaza study "in patients with severe hypertriglyceridemia, type IV, with 500 < TG < 2000 mg/dl").)

A POSA would have understood that Hayashi includes at least one patient with triglyceride levels > 500 mg/dL in light of Hayashi's data. (ECF No. 367 at 725:21-727:1.) Table I reports that at baseline, the patients in the study had a triglyceride level of 300 ± 233 mg/dl. (Ex. 1532 at 5.) Dr. Heinecke[11] explained that while "there is some ambiguity in this paper about what the meaning is of the plus minus 233[,] . . . overwhelmingly, in the medical literature, that would be a standard deviation." (ECF No. 367 at 725:21-727:1.)

The standard deviation is the average spread of the data around the mean value of 300 mg/dl (for a normal distribution of data, two-thirds of the data points are within one standard deviation of the mean). (*Id*.) Accordingly, as Dr. Heinecke explained, "[b]ecause there's a value of plus or minus 233, there was at least one patient in that study who had a value of greater than 300, and because that's only encompassing two-thirds of the data, one-sixth of the patients would likely have been above 533." (*Id*.) Although Dr. Lavin initially told the PTO[12] that not even one patient in Hayashi would have had triglyceride levels > 500 mg/dL, Dr. Lavin later testified that he would "rewrite" his declaration on this point, explaining that in Hayashi "you know that there must be at least one subject" with triglyceride levels > 500 mg/dL, and that it is "likely that you have one or two observations

[11]Defendants' invalidity expert.

[12]Plaintiffs submitted a declaration from Dr. Lavin to overcome an initial rejection for obviousness of the '889 Application. (*See* ECF No. 324 at 16-18 (stipulating to facts providing more details about these interactions).)

above 533." (Lavin Dep. Tr. at 102:24-103:21.) Dr. Toth[13] did not "offer any type of statistical opinion to corroborate what Dr. Lavin told the patent office." (ECF No. 371 at 1868:13-16.)

Dr. Heinecke explained that there is an alternative theory that Hayashi's reference to 300 ± 233 mg/dl instead refers to the range of triglyceride values, rather than the standard deviation. (ECF No. 367 at 725:21-727:1.) But "this would be very unusual," and in any case, under that interpretation there would still be "at least one patient in the study that had a value of 533." (*Id*.) Therefore, under either interpretation of Hayashi, at least one patient had triglyceride levels > 500 mg/dL. (*Id.* at 727:2-6.)

Hayashi discloses that "[a]fter 8 weeks, patients treated with ethyl icosapentate showed significant reductions in . . . triglyceride (41%)," and reports reductions in LDL-C (7%) and apolipoprotein B (7%), which was not statistically significant. (Ex. 1532 at 5.) Hayashi therefore concludes that "[p]urified icosapentate (1800 mg/d for 8 weeks) decreased total cholesterol and triglyceride in patients with FCH (Table I)," and that "[n]o overt effects of icosapentate on plasma LDL-C and HDL-C were seen, although a decrease in LDL-C was noted (Table I)." (*Id.* at 7.)

Hayashi does not report the LDL-C data of patients with triglycerides > 400 mg/dL because Hayashi used the Friedewald equation to calculate LDL-C levels. (*Id.* at 5; *see also* ECF No. 367 at 798:23-800:7.) The Friedewald equation is commonly used in clinical studies to calculate LDL-C levels and operates by using triglyceride levels to estimate LDL-C levels, but "is not accurate for triglycerides above 400 milligrams per deciliter." (ECF No. 367 at 798:23-800:7.) But while Hayashi does not report LDL-C data in patients with triglycerides > 400 mg/dL, Hayashi does not limit its conclusion regarding EPA's effects on LDL-C levels to patients with lower triglyceride levels. Hayashi concludes that "[a]lthough the effects of fish oils on plasma LDL-C and HDL-C are complex, judging from the present study, purified icosapentate apparently has no deleterious effect on plasma

[13]Plaintiffs' invalidity expert.

LDL-C or HDL-C in patients with FCH." (Ex. 1532 at 7.) Again, some patients with FCH—including at least one patient in the Hayashi study—have triglyceride levels above 500 mg/dL. (*Id.*; *see also* ECF No. 367 at 725:21-727:1; Lavin Dep. Tr. at 102:24-103:21.)

e) Kurabayashi (2000)

Kurabayashi, *et al.*, *Eicosapentaenoic Acid Effect on Hyperlipidemia in Menopausal Japanese Women*. Obstet. Gynecol. 96:521-8 (2000) ("Kurabayashi") was published in 2000 and is prior art to the patents-in-suit.

Kurabayashi investigated the effects of administering purified EPA (96.5% EPA) at a dose of 1.8 g/day in combination with estriol (the "EPA group") as compared to estriol therapy alone (the "control group") for forty-eight weeks to hyperlipidemic, menopausal women. (Ex. 1534 at 1.) Estriol is a form of estrogen that is commonly used in menopausal women to alleviate the symptoms of menopause. (ECF No. 367 at 735:2-20.) As an estrogen, estriol is known to elevate triglyceride levels. (*Id.*)

Despite coadministration with estriol, Kurabayashi reports a statistically significant 27% reduction in triglyceride levels in the EPA group. (Ex. 1534 at 3.) As compared to the

control group, the EPA group experienced a statistically significant reduction in triglyceride levels at the 12, 24, and 48-week checkpoints:

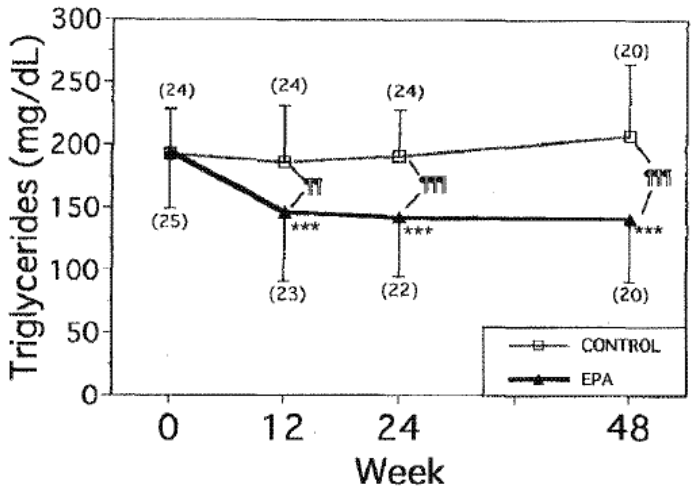

Figure 2. Changes in serum triglycerides levels from baseline to week 48 in the control and eicosapentaenoic acid groups in women whose level of triglycerides was not less than 150 mg/dL at baseline. Abbreviations as in Figure 1. Data are mean ± standard deviation. Numbers in parentheses indicate number of samples. ***$P < .005$ (versus baseline as calculated by Student paired t test). ¶¶$P < .01$. ¶¶¶$P < .005$ (intergroup differences were assessed by Student unpaired t test).

(*Id.* at 4.) Kurabayashi further reports that "[l]ow-density lipoprotein cholesterol levels in both groups were significantly lower." (*Id.* at 3.)

Kurabayashi further reports a statistically significant reduction in Apo B levels in the EPA group of 6.9%. (*Id.* at 4-5.) With a p-value of < .001, EPA's effects on Apo B were highly significant. (*Id.*; *see also* ECF No. 367 at 737:1-23.) In contrast, Kurabayashi reports a non-statistically significant 1.5% reduction in Apo B levels in the control group:

Table 3. Changes in Serum Levels of Apolipoprotein, Lipoprotein(a), and Remnant Lipoprotein

	Baseline	Week 12	Week 24	Week 48	% change at week 48	P*
n (Control/EPA)	72/69	69/63	66/59	63/55		
Apolipoprotein A-I (mg/dL)						
Control group	153.5 ± 26.3	152.7 ± 27.7	150.0 ± 25.2	150.6 ± 24.1	−1.9	NS
EPA group	152.1 ± 31.6	149.5 ± 28.6	148.2 ± 25.4	150.7 ± 28.5	−0.9	NS
p†	NS	NS	NS	NS		
Apolipoprotein A-II (mg/dL)						
Control group	36.7 ± 4.0	37.5 ± 4.8	36.8 ± 5.2	35.6 ± 5.5	−3.0	NS
EPA group	36.8 ± 6.3	35.3 ± 5.4	34.8 ± 5.3	34.1 ± 5.8	−7.3	.004
p†	NS	.01	.04	NS		
Apolipoprotein B (mg/dL)						
Control group	123.4 ± 18.5	121.9 ± 21.0	121.6 ± 20.1	121.5 ± 18.6	−1.5	NS
EPA group	124.8 ± 18.7	119.4 ± 21.5	119.3 ± 20.4	116.2 ± 19.3	−6.9	< .001
p†	NS	NS	NS	NS		

(Ex. 1534 at 5; *see also* ECF No. 367 at 737:1-23.)

The results reported in Kurabayashi do not suggest any interaction or synergy between EPA and estriol. (ECF No. 367 at 735:21-736:9.) Instead, synergy is usually only seen between drugs that have similar effects, such as two drugs that reduce blood pressure. (*Id.*)

In light of the statistically-significant differential effects reported between the EPA and control groups, a POSA would have attributed the reduction in Apo B to EPA. (*Id.* at 737:24-738:8.)

f) Rambjør 1996

Plaintiffs rely on Rambjør to argue that a POSA would have understood that EPA increased, not decreased, LCL-C levels. (ECF No. 377 at 224-26.) Rambjør reports that EPA "produced significant decreases in both TG and very low density lipoprotein (VLDL) cholesterol," but was also associated with a statistically significant "increase[] in low density lipoprotein cholesterol levels." (Ex. 1961 (Rambjør, *et al.*, *Eicosapentaenoic Acid Is Primarily Responsible for Hypotriglyceridemic Effect of Fish Oil in Humans*, 31 Lipids S-45 (1996) ("Rambjor")) at 3.) But Rambjor used only 3 g/day of EPA that was only 91% pure. (*Id.*) Because "omega-3s are complex," Dr. Toth testified that a skilled artisan "would have no idea" what fatty acids are in the other 9%, which could have included a substantial amount of DHA. (ECF No. 371 at 1814:17-22.)

Rambjor does not appear authoritative for other reasons as well. Rambjor consolidated data from three separate studies, and only included 9 patients in the DHA group. (Ex. 1961 at 4.) Rambjor further only included a 2-week washout period, and patients were only given EPA or DHA for a period of 3 weeks. (*Id.* at 3.) The Rambjor study was therefore underpowered, and its design of comparing the effects of two drugs with a significantly different number of subjects in each group was unusual. (ECF No. 367 at 782:4-783:1.) Rambjor itself concluded that "[f]urther studies are needed to clearly define individual effects of EPA and DHA on human lipid metabolism." (Ex. 1961 at 6.)

Mori is "one of those further studies" that clearly defined the individual effects of EPA and DHA on human lipid metabolism. (ECF No. 371 at 1842:10-17.) Mori, which published after Rambjor, criticized Rambjor's design as studying "only a small number of subjects in the DHA group," for being of "short duration," and for including "only a 2-wk washout period between treatments." (Ex. 1538 at 5, 9.) In contrast to Mori—which studied the claimed EPA dose and purity (4/g day at 96% purity), (Ex. 1538 at 2)—the EPA studied in Rambjor was only 91% pure and administered at only 3 g/day (Ex. 1961 at 3; *see also* ECF No. 371 at 1841:7-1842:1). A POSA as of March 2008 thus would have relied on the teachings of Mori over those in the earlier Rambjor reference—particularly if the skilled artisan were focusing on a dose of 4 g/day and at least 96% purity, as used in Mori but not in Rambjor. (ECF No. 367 at 784:22-785:2.) This is evidenced by the fact that Mori has been repeatedly cited in the literature, including Plaintiffs' internal documents and submissions to the FDA, but Plaintiffs have not identified any trial exhibit that cites Rambjor other than von Schacky, discussed below. (*See, e.g.*, Ex. 1816 at 68 (summarizing over a dozen prior-art EPA studies to FDA, including Mori but not Rambjor); Ex. 1800 at 12-13 (summarizing DHA and EPA's effects on LDL-C in an investor presentation and citing Mori but not Rambjor).)

g) Von Schacky (2006)

Another reference relied on by Plaintiffs (*see, e.g.*, ECF No. 377 at 226-229), von Schacky, did not report any primary data on EPA or DHA's effects, but reported in a table

that studies suggested that both EPA and DHA increase LDL-C. (Ex. 1605 (von Schacky, *A review of omega-3 ethyl esters for cardiovascular prevention and treatment of increased blood triglyceride levels*, Vascular Health and Risk Management 2(3):251-262 (2006) ("von Schacky")) at 9; *see also* ECF No. 371 at 1844:9-14.) The table, however, merely included arrows pointing in different directions and did not attribute any significance to any of the variables reported. (Ex. 1605 at 9; *see also* ECF No. 367 at 785:23-786:22.)

Von Schacky further reported inconsistent information, citing Mori and claiming that "[i]n more recent comparative studies, no effects of either EPA or DHA . . . were seen on LDL levels." (Ex. 1605 at 5.) But as Dr. Toth conceded, "[t]hat's not what Mori said." (ECF No. 371 at 1847:8-17.) Mori expressly reports that "[s]erum LDL cholesterol increased significantly with DHA (by 8%; P = 0.019)." (Ex. 1538 at 1.) Because von Schacky is a review article, a skilled artisan also would have looked at the underlying clinical studies cited by von Schacky, including Mori. (ECF No. 371 at 1848:4-8.)

In any event, as Dr. Heinecke explained, because EPA is LDL-neutral, one would expect to see small increases or decreases across studies due to chance alone. (ECF No. 367 at 740:18-25.) Therefore, if among the available literature on EPA's effects on LDL-C one saw "one-third of the studies showing an increase, one-third of the stud[ies] showing a decrease, and one third of the stud[ies] showing no effect, that would be very strong evidence that there was no overall effect on the intervention." (*Id*. 781:21-782:3.)

2. Level of Ordinary Skill in the Art

The determination of obviousness must be done based on the knowledge possessed by one of ordinary skill in the art at the time the invention was made. The Asserted Claims and the prior art are evaluated at the time of the invention from the standpoint of a POSA. A POSA is a hypothetical person who is presumed to have access to, and be aware of, all of the relevant prior art at the time of the invention. *See, e.g.*, *Rothman v. Target Corp.*, 556 F.3d 1310, 1318 (Fed. Cir. 2009). Factors that may be considered in determining the level of ordinary skill in the art may include: (1) type of problems encountered in the art; (2) prior art solutions to those problems; (3) rapidity with

which innovations are made; (4) sophistication of the technology; and (5) educational level of active workers in the field. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). Thus, it is not permissible to use hindsight after viewing the claimed invention to determine questions of obviousness or to rely at all on the teachings of the claimed invention in determining whether one of ordinary skill in the art would find the invention obvious. *See, e.g.*, *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1367 (Fed. Cir. 2017) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.") (quoting *Otsuka Pharm. Co. v. Sandoz, Inc*., 678 F.3d 1280, 1296 (Fed. Cir. 2012)).

Plaintiffs and Defendants proposed different definitions of the POSA, but those differences are not material because both sides made clear their arguments apply with equal force regardless of the definition the Court adopts. (ECF Nos. 373 at 64-65, 377 at 173-174.) The Court therefore assumes without deciding that one of the two definitions that follow below applies to its conclusions of law.

Plaintiffs proposed the following definition. (ECF No. 377 at 173-174.) The POSA in this case world be (1) a clinician with an M.D., or D.O. and at least 2 to 3 years of experience in the diagnosis, evaluation, and treatment of lipid blood disorders, including severe hypertriglyceridemia (*i.e.*, TG levels of at least 500 mg/dl), or (2), alternatively, a clinician, such as a nurse practitioner or physician's assistant, with 3 to 5 years of experience in the diagnosis, evaluation, and treatment of lipid blood disorders, including severe hypertriglyceridemia. (*See id.*)

Defendants proposed the following definition. (ECF No. 373 at 64-65.) "[T]he POSA to whom the patents in-suit are directed would have had (a) at least a medical degree or an advanced degree in the field of lipid biochemistry; (b) several years of experience in the development and/or clinical use of fatty acids to treat blood lipid disorders, including fish oil based fatty acids, *i.e.*, EPA and DHA, and their dosage forms; and (c) access to a

team including one or more of a medical doctor, an analytical chemist, or a pharmaceutical chemist."[14] (*Id.* at 64.)

3. Differences between the Prior Art and the Claims at Issue

The primary difference between the prior art and the Asserted Claims is that the Lovaza PDR, Defendants' principal prior-art reference, used a mixture of DHA and EPA, while the Asserted Claims involve a pharmaceutical composition containing purified EPA, but substantially no DHA. Defendants additionally point to other pieces of prior art to explain why the Other Health Benefit Claims were obvious.

Here, all 10 Asserted Claims recite the same method of treatment—namely, a method of reducing triglycerides in a patient with triglycerides of at least 500 mg/dL by administering, for at least 12 weeks, about 4 g/day of at least 96% purified EPA. (Ex. 1500 ('728 patent claims 1 and 16); Ex. 1502 ('715 patent claim 14); Ex. 1504 ('677 patent claims 1 and 8); Ex. 1506 ('562 patent claim 1); Ex. 1514 ('560 patent claims 4 and 17); Ex. 1516 ('929 patent claims 1 and 5).) The Lovaza PDR taught a method of treating patients with triglycerides of at least 500 mg/dL by administering, for at least 12 weeks, 4 g/day of a mixture of EPA and DHA. (Ex. 1535 at 2-3.)

The Lovaza PDR warned, however, that this method of treatment could substantially increase patients' LDL-C levels (at least at a median triglyceride level of 816 mg/dL), which was undesirable. (*Id.* at 3.) Mori taught that DHA increased LDL-C, whereas 4 g/day of 96% purified EPA reduced triglycerides without increasing LDL-C. (Ex. 1538 at 2-3.) Other prior art (*e.g.*, Kurabayashi and Hayashi) similarly taught that EPA did not increase LDL-C in patients with triglyceride levels up to 400 mg/dL. (ECF No. 367 at 715:10-716:4, 759:10-760:1.)

[14]Though, as stated, the Court does not choose between the two definitions of the POSA proposed by the parties, Defendants' proposed definition strikes the Court as more reasonable because it appears calculated to include a person who develops drugs, rather than merely people who would be able to treat a blood lipid disorder like Plaintiff's definition does. The key obviousness disputes in this case focus on drug development, not merely treatment, of blood lipid disorders.

4. Secondary Considerations

The Court's obviousness inquiry must also consider whether objective indicia of non-obviousness support the Asserted Claims. "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966); *see also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (explaining that objective evidence of nonobviousness may include copying, long-felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans). The Court discusses below its factual findings relevant to its analysis of secondary considerations included in its conclusions of law further below.

a) REDUCE-IT

Plaintiffs point to the results of the REDUCE-IT study as objective evidence of nonobviousness. (ECF No. 379 at 35-37.) The REDUCE-IT study was "a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting baseline triglyceride level of 135 to 499" mg/dl and a fasting baseline LDL-C level of 41 to 100 mg/dl. (Ex. 1641 at 1 (the "Bhatt Article").)

Each subject in REDUCE-IT had a fasting baseline triglyceride level of 135 to 499 mg/dl. (*Id.* at 2.) "[B]ecause of the intraindividual variability of triglyceride levels, the initial protocol allowed for a 10% lower triglyceride level from the target lower limit, which permitted patients to be enrolled if they had a triglyceride level of at least 135 mg per deciliter." (*Id.*) In May 2013, the first protocol amendment "changed the lower limit of the acceptable triglyceride level from 150 mg per deciliter to 200 mg per deciliter, with no allowance for variability." (*Id.*)

Nevertheless, there was a substantial fraction of patients in the REDUCE-IT Study with median triglyceride values <150 mg/dL during the study, given that the inclusion

criteria for triglycerides was limited to the screening exam for entry into the study and because triglyceride levels can vary over a wide range. More specifically, about 10% of subjects had triglyceride levels below 150 mg/dl, about 30% had triglyceride levels between 150 and 200 mg/dl, and the remaining subjects had triglyceride levels about 200 mg/dl. (*Id.* at 4, Table 1.)

While a small subset of patients had triglyceride levels that rose above 500mg/dl at some point in time during the REDUCE-IT study due to intraindividual variability, "REDUCE-IT focused on patients with triglycerides below 500." (ECF No. 371 at 1894:12-14.) Again, "eligible patients . . . had to have a fasting triglyceride level of 150 to 499 milligrams per deciliter. This is less than 500 milligrams per deciliter." (ECF No. 367 at 818:18-21.) Thus, REDUCE-IT was not "designed to evaluate patients [with] triglycerides above 500" and did not include any patients with a baseline triglyceride level of 500 mg/dl or above. (*Id.* at 819:14-16.) Dr. Budoff agreed that "REDUCE-IT focused on a different patient population than the patient population" for Defendants' labels. (ECF No. 366 at 530:16-19.) In fact, the MARINE study and REDUCE-IT study, and thus the related indications, involved "completely different patient populations." (*Id*. at 589:21-1.)

Additionally, "[a]ll the patients in REDUCE-IT were taking statins." (ECF No. 371 at 1896:15-17.) More specifically, "[e]ligible patients . . . had been receiving a stable dose of a statin for at least 4 weeks." (Ex. 1641 at 2; *see also* ECF No. 367 at 821:9-22.) Thus, "in REDUCE-IT, we're talking about patients who are already on a statin for controlling their bad cholesterol." (ECF No. 365 at 271:10-13.) "REDUCE-IT did not have a monotherapy arm," *i.e.* an arm with patients not taking a statin. (ECF No. 371 at 1897:5-7.) In fact, "it would have been unethical to have just a Vascepa monotherapy arm. The FDA would never allow it because statin therapy is the standard of care for patients in secondary prevention for high risk diabetic patients." (*Id.* at 1897:7-10.) And approximately 58.6% of the patients enrolled in the treatment arm of the REDUCE-IT Study were diabetics. (Ex. 1641 at 4, Table 1.)

Patients in REDUCE-IT were randomly assigned to receive either 4 g/day of Vascepa or placebo (mineral oil). (*Id.* at 1-2.) "The primary efficacy end point was a composite of cardiovascular death, nonfatal myocardial infraction (including silent myocardial infarction), nonfatal stroke, coronary revascularization, or unstable angina in a time-to-event analysis." (*Id.* at 3.) "The key secondary end point [was] a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis." (*Id.* at 3.) A total of 8179 patients were enrolled and were followed for a median of 4.9 years. (*Id.* at 1, 5.)

"The median change in triglyceride level from baseline to 1 year was a decrease of 18.3% . . . in the icosapent ethyl group and an increase of 2.2% . . . in the placebo group." (*Id.* at 5.) The median reduction [in triglyceride level] from baseline . . . was 19.7% greater in the icosapent ethyl group than in the placebo group." (*Id.*) "Baseline triglyceride levels (≥ 150 vs. <150mg per deciliter or ≥200 or < 200 mg per deciliter) had no influence on the primary or key secondary efficacy end points." (*Id.* at 7.) "The attainment of triglyceride levels of 150 mg per deciliter or higher or below 150 mg per deciliter at 1 year after randomization also had no influence on the efficacy of icosapent ethyl as compared with placebo with respect to the primary or key secondary efficacy end point." (*Id.*)

Thus, the REDUCE-IT benefits "occur[ed] irrespective of the attained triglyceride level," and "the cardiovascular risk reduction was not associated with attainment of a more normal triglyceride level." (*Id.* at 10; *see also* ECF No. 367 at 817:2-5.) As Dr. Toth pointed out, "even if [a subject] didn't normalize [their] triglycerides in [the] trial, [they would] still derive a benefit." (ECF No. 370 at 1624:18-20.) With respect to LDL-C levels, "[t]he median change in LDL cholesterol level from baseline was an increase of 3.1% . . . in the icosapent ethyl group and an increase of l0.2% . . . in the placebo group." (Ex. 1641 at 5.) REDUCE-IT "found no substantial difference in the benefit" of EPA based on whether patients "had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels." (*Id.* at 7.) Thus, "[t]here was no relationship to the change in LDL

cholesterol levels to the benefit in terms of cardiovascular risk reduction." (ECF No. 367 at 820:22-24.)

In November 2018, Plaintiffs announced that REDUCE-IT identified a cardiac benefit in patients receiving Vascepa as compared to placebo. The results show that "[a] primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group." (Ex. 1641 at 1.) "A key secondary efficiency end-point event . . . occurred in 11.2% of the patients in the icosapent ethyl group, as compared with 14.8% of the patients in the placebo group." (*Id.* at 5.) The rate of cardiovascular death was 4.4% in the icosapent ethyl group and 5.2% in the placebo group. (*Id.* at 7.) According to the Kaplan-Meier plots—which demonstrate results for certain time intervals—in the Bhatt Article, the cardiac benefits were not observed until patients had been taking 4 g/day of Vascepa for a year or more. (*Id.* at 5.)

In other words, there is no "evidence that the cardiovascular risk reduction in REDUCE-IT occurs within 12 weeks . . . Instead there is no divergence [between the treated group and placebo group] in terms of cardiovascular risk until year one, and that difference did not become statistically significant until year two." (ECF No. 367 at 819:22-24.) Thus, "it takes time to accrue the [cardiovascular benefit], and if you stop it at four months . . . then you're going to lose that benefit." (ECF No. 371 at 1896:10-14.)

Based on these REDUCE-IT results, FDA approved Vascepa to reduce the risk of "myocardial infraction, stroke, coronary revascularization, and unstable angina requiring hospitalization" in patients that had "elevated triglyceride (TG) levels (≥ 150 mg/dL)," and either an "established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." (Ex. 2248 at 1.)

"Amarin has separate patents covering the method used in the REDUCE-IT study . . . [and] those patents are not being asserted in this case." (ECF No. 371 at 1895:4-10.) Amarin submitted a Form 3542a for the REDUCE-IT sNDA. (Ex. 2250.) Through this form, Plaintiffs represented to FDA that only the patents listed relate to Vascepa's REDUCE-IT indication. (Ex. 2299.) None of the asserted patents were listed. If Plaintiffs believed that

the asserted patents claimed "a method of using [Vascepa] that is the subject of" the REDUCE-IT indication, they would have had to list those patents on the Form 3542a included with their sNDA. (Ex. 2250.) *See also* 21 C.F.R. § 314.53(b). As discussed above, there is no overlap between the patents listed for the REDUCE-IT indication and the asserted patents. (Ex. 2299.)

b) Commercial Success

The parties dispute whether Vascepa, which embodies the Asserted Claims, is a commercial success. Predictably, Plaintiffs argue it is (ECF No. 379 at 37-38), Defendants argue it is not (ECF No. 378 at 32). The parties also presented competing expert testimony on this topic at Trial. (ECF No. 369.) Having considered the expert testimony and other evidence presented by both sides, the Court finds Plaintiffs' argument—that Vascepa is a commercial success—more persuasive.

More specifically, substantial and sustained increases in Vascepa prescriptions, net sales, and market share, as well as Vascepa's positive net present value ("NPV"), demonstrate that Vascepa is a commercial success. (ECF No. 369 at 1423:3-15.)

Prescriptions for Vascepa have grown substantially since the product's launch in January 2013. 174,000 prescriptions for Vascepa were filled in 2013, and the number increased every year, reaching 1.3 million prescriptions in 2018, an average annual increase of about 50%. (*Id.* at 1427:9-17.) This increase indicates that patients and health insurers are willing to pay a premium for the features of Vascepa, given that a relatively inexpensive generic version of Lovaza has been available since 2014. (*Id.* at 1427:18-1428:3.)

Vascepa's net sales have also grown substantially since the product's launch. Vascepa's net sales were $26 million in 2013 and have increased every year, reaching $228 million in 2018, an average annual increase of 54%. (*Id.* at 1429:2-9.) The increase indicates that the product is providing value and that patients and health insurers are willing to pay a premium for the features of Vascepa. (*Id.* at 1429:10-15.) Moreover, the Court finds Defendants' contention that Vascepa's sales are driven by rebates and

discounts unpersuasive. (ECF No. 373 at 113.) The net sales metric relied upon by Dr. Nicholson already accounts for all rebates and discounts. (ECF No. 369 at 1304:17-23, 1429:22-1430:5, 1431:3-14.) In any case, the level of rebates and discounts provided for Vascepa is in line with the industry norm. (*Id.* at 1431:3-14, 1433:12; *see also* Ex. 746 at 5, 10.)

Vascepa's share of the market for omega-3 fatty acid drugs has also grown every year since its launch. Vascepa's share of omega-3 fatty acid prescriptions was 4% in 2013, increasing to 32% in 2018. (ECF No. 369 at 1435:3-16.) In contrast, branded Lovaza's share of the same market decreased from approximately 96% in 2013 to under 5% in 2018. (*Id.* at 1436:19-1437:7.) Vascepa's share of the broader market for TG-reducing drug prescriptions also increased from 1% in 2013 to 6% in 2018. Vascepa's increasing market share is a strong indicator of its increasing value over time. (ECF No. 369 at 1434:8-24, 1435:17-1436:3.) In fact, every other TG-reducing drug's prescriptions were decreasing from 2013 to 2018, whereas Vascepa's prescriptions increased in the same period. That Vascepa has bucked the trend speaks highly of its performance in the market. (*Id.* at 1438:7-18.)

Vascepa's NPV also demonstrates its commercial success. NPV is the most common method that pharmaceutical companies use to determine whether to launch a new product and to track whether the product is successful. (*Id.* at 1440:1-15, 1444:22-1445:1, 1469:20-1470:7; *see also* Ex. 600 at 2, 5; Ex. 602 at 5.) A positive NPV means that the product is more profitable than the average for similar products in the industry. (ECF No. 369 at 1440:16-1441:14, 1443:18-21; Ex. 602 at 10 ("Any time you find and launch a positive NPV project, a project with present value exceeding its required cash outlay, you have made your company's stockholders better off."). Vascepa's NPV is expected to be zero in 2024, which means that its investors will have recouped their investment and received the industry average return in Vascepa's twelfth year in the market. (ECF No. 369 at 1458:5-20.) Over its entire lifecycle, Vascepa is expected to have

a positive NPV of $1.9 billion, which means that it will deliver a return that exceeds the industry average by $1.9 billion. (*Id.* at 1458:21-1459:4.)

Defendants' contention that Vascepa is not a commercial success is largely based on the theory that Vascepa did not make a profit in its first six years on the market. But Defendants ignore the reality that drugs have long lifecycles, the beginning of which involves spending vast amounts of money on R&D. (*Id.* at 1441:15-1442:7; *see also* Ex. 612 at 2.) Here, Plaintiffs spent $465 million in research and development between 2008 and 2018. (ECF No. 369 at 1426:17-24.) Moreover, marketing spending tends to be higher at the beginning of a pharmaceutical product's lifecycle, given the need to educate physicians about the clinical profile of the new drug in question. (*Id.* at 1306:11-1307:2, 1471:7-1472:1.) At the same time, it can take as long as 12 years for new drugs in the top ten percent of sales to achieve peak sales. (*Id.* at 1468:11-1469:4; *see also* Ex. 607 at 20.) Indeed, a study has shown that it took drugs 16 years on average to reach NPV of zero. (ECF No. 369 at 1469:20-1470:7; *see also* Ex. 612 at 6.) Therefore, the pharmaceutical industry considers the entire lifecycle of a drug in analyzing commercial success rather than just the first six years after the drug's launch. (ECF No. 369 at 1445:23-1446:19, 1468:11-1469:4, 1512:17-24; *see also* Ex. 600 at 2.) Defendants' alternative approach, which relies on taking a snapshot of Vascepa's performance after Plaintiffs have incurred the vast majority of the R&D spending, but before they have enjoyed the fruits of that spending, is less persuasive in light of the testimony at Trial regarding industry practice.

Defendants also contend that Dr. Nicholson's NPV analysis is unreliable because it was excessively influenced by the one of the five forecasts upon which he relied. Defendants' contention is unpersuasive. The forecast in question is from a firm called H.C. Wainwright, which (as the evidence showed) does not have a history of systematically overestimating Amarin's revenue or profit. (ECF No. 369 at 1460:22-1463:18; *see also* Ex. 752 at 2; Ex. 637 at 63; Ex. 658 at 3; Ex. 724 at 4.) In any event, Vascepa's NPV is expected to be positive whether or not H.C. Wainwright's forecast is included. (ECF No.

369 at 1465:3-10, 1504:1-16, 1521:6-18.) This shows that Dr. Nicholson's NPV analysis is robust and reliable. Dr. Nicholson's NPV analysis is also consistent with Defendant Hikma's own January 2020 presentation to investors, which ranks Vascepa as having the fourth highest U.S. market size among all the drugs in Hikma's generic pipeline. (Ex. 1218 at 12.) In sum, the Court finds that Vascepa is a commercial success.

c) Praise

Plaintiffs also argue that praise for Vascepa weighs in favor of finding the Asserted Claims nonobvious. (ECF No. 377 at 269-271.) However, the Court finds that the evidence Plaintiffs proffer to show praise is more qualified and equivocal than Plaintiffs represent in their briefing. Thus, the Court finds Plaintiffs' proffered evidence of praise does not weigh in favor of finding the Asserted Claims nonobvious.

Plaintiffs' expert Dr. Toth cited several articles as purported evidence of such praise at Trial, but none of them support his opinion. (ECF Nos. 370 at 1722:15-5, 371 at 1848:11-20.) First, Dr. Toth cited the O'Riordan article, which quoted several doctors on the results of MARINE. (Ex. 1581.) Specifically, Dr. Toth cited a statement by Dr. McGuire that "if you can have favorable cardiovascular effects without raising LDL cholesterol, that's going to be an advantage," and a statement by Dr. Nissen that this "gives you all the benefit without the downside." (*Id.* at 1-2; *see also* ECF No. 370 at 1606:24-1612:24.) But as the article reveals, neither doctor gave unmitigated praise; both expressed caveats about those statements. Dr. McGuire "was cautious in interpreting the results" of MARINE, "insert[ed] a dose of caution," and made clear that his focus was on "cardiovascular effects," not just triglyceride reduction. (Ex. 1581 at 1.) If anything, Dr. McGuire saved his praise for "trials such as Japan EPA Lipid Intervention Study ([")]JELIS[")])," which actually "showed a favorable signal of reduced cardiovascular events." (*Id.*) Similarly, Dr. Nissen "expressed the same caveats" about MARINE, and noted that he "would like to eventually see a head-to-head comparison between Lovaza" and Vascepa, which to date has never been done. (*Id.* at 2.) Even apart from these caveats, Dr. Toth ignored the statement by Dr. Blumenthal, which O'Riordan also reported. As discussed above, Dr. Blumenthal did

not praise Vascepa or MARINE, but instead dismissed MARINE's significance because typical increases in LDL-C with Lovaza were "'modest' and 'not that big an issue,'" especially since Lovaza "works well with statins." (*Id.* at 2.) Given these conflicting statements, O'Riordan as a whole does not suggest that Vascepa's ability to avoid increases in LDL-C has been praised by the industry.

Second, Dr. Toth relied on articles by Fialkow (Ex. 852) and Castaldo (Ex. 866). (ECF No. 370 at 1612:25-1615:13.) But those articles merely state the fact that Vascepa does not increase LDL-C—they do not praise Vascepa for that reason (or indeed, for any reason). The statement that Dr. Toth quoted from Fialkow states that "treatment with the EPA-only product, icosapent ethyl [i.e., Vascepa] has no LDL-C monitoring requirement." (Ex. 852 at 5.) Similarly, the statement that Dr. Toth quoted from Castaldo states that Vascepa "does not increase LDL-C levels, as supported by clinical studies and the icosapent ethyl product label." (Ex. 866 at 6.) These matter-of-fact observations, which merely repeat information from the Vascepa product label and the MARINE trial, do not praise Vascepa or the claimed invention. As the Federal Circuit has made clear, such "journal citations that reference the findings stated in [the patentee's] published efficacy studies . . . fall well short of demonstrating true industry praise." *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013).

Third, Dr. Toth relied on an Amarin-sponsored article in which Dr. Bays said that MARINE's results were "surprising." (ECF No. 371 at 1848:11-20 (referring to Ex. 833 at 6).) The Federal Circuit has made clear, however, that such "self-referential commendation [also] fall[s] well short of demonstrating true industry praise." *Bayer*, 713 F.3d at 1377; *see also In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016) (rejecting patentee's reliance on "self-serving statements from researchers about their own work" as alleged evidence of praise).

In sum, Plaintiffs have not produced evidence that the industry "praised" the claimed invention for avoiding an increase in LDL-C. Thus, the Court finds as a factual

matter that Plaintiffs' proffered evidence of praise does not support its nonobviousness arguments discussed in more detail in the Court's conclusions of law below.

IV. CONCLUSIONS OF LAW

The Trial focused on induced infringement[15] and whether the Asserted Patents are invalid as obvious in light of the prior art. The Court first addresses infringement below, and then obviousness.

A. Infringement

1. Legal Standard

"Infringement is a two-step inquiry, in which a court must first construe disputed claim terms, and then compare the properly construed claims to the accused device." *Nazomi Commc'ns, Inc. v. Arm Holdings, PLC*, 403 F.3d 1364, 1367-68 (Fed. Cir. 2005) (citation omitted). The first step as to Plaintiffs' allegations that Defendants' proposed products as they will be prescribed infringe the Asserted Claims is already complete—the Court has construed the disputed claim terms. (ECF No. 135.) Plaintiffs bear the burden of persuasion as to infringement and must therefore prove all facts necessary to support their infringement claim. *See Medtronic, Inc. v. Mirowski Family Ventures, LLC*, 571 U.S. 191, 198 (2014) ("It is well established that the burden of proving infringement generally rests upon the patentee."). Further, "[i]nfringement is a question of fact." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1040 (Fed. Cir. 2016) (citation omitted).

In this type of Hatch-Waxman Act patent litigation, where Defendants have filed ANDAs, the question of whether Defendants may be held liable for inducing infringement turns on whether Defendants "have the specific intent, based on the contents of their proposed labels, to encourage physicians to use their proposed ANDA products" in a way that infringes the Asserted Claims. *Grunenthal GMBH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1339 (Fed. Cir. 2019) (citation omitted). In other words, the Court must ask "whether the

[15]While Plaintiffs initially asserted two indirect infringement theories, the Court granted summary judgment to Defendants on Plaintiffs' contributory infringement theory. (ECF No. 278 at 11-13.)

label encourages, recommends, or promotes infringement." *Id.* (citation omitted). And because the Asserted Claims are method claims, the "pertinent question is whether the proposed label instructs users to perform the patented method." *Id.* (citation omitted).

Plaintiffs have argued at various points in this case that they need only show Defendants' labels will "inevitably lead some physicians to infringe" to establish Defendants' inducement liability. (*See, e.g.*, ECF No. 327 at 19 (citing *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1369 (Fed. Cir. 2017).) Defendants counter that labels permitting or even describing an infringing use are insufficient for finding inducement unless those labels "specifically encourage" or "require" infringement. (ECF No. 332 at 17-18.) The Court agrees with Defendants on this point. The fact that some physicians will infringe when they read and follow the labels is necessary, but not sufficient to show inducement based on those labels. *See Grunenthal*, 919 F.3d at 1339 (finding no inducement where the defendants' proposed ANDA labels did not "specifically encourage" using the patented drug in an infringing way); *HZNP Medicines LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019) ("the mere existence of direct infringement is not sufficient for inducement[,] [i]nstead, our inquiry focuses on whether the instructions reflect an affirmative or specific intent to encourage infringement.") (internal quotation marks, punctuation, and citation omitted).[16] Thus, the Court's inducement inquiry focuses on Defendants' proposed labels, specifically whether they encourage, recommend, or promote infringement. *See Grunenthal*, 919 F.3d at 1339.

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[16] *Grunenthal* distinguished *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1059-60 (Fed. Cir. 2010), which Plaintiffs also relied on at Trial in support of an effectively lower inducement burden, because there "the defendant proceeded with a plan to distribute the generic drug knowing that its label posed infringement problems." *Grunenthal*, 919 F.3d at 1340. Both in *Grunenthal* and in this case, the parties relied only on the indications of the proposed labels, making *AstraZeneca* inapposite. *See id.*

2. Discussion

Though the Court agrees with Defendants' view of the induced infringement legal standard, it disagrees with Defendants' application of it. (ECF No. 378 at 12-19 (arguing against Plaintiffs' induced infringement theory).) To the contrary, the Court finds Plaintiffs carried their burden at Trial to show Defendants' proposed labels[17] will induce infringement of the Asserted Claims.

The focal point of the Court's decision is the Clinical Studies section of the labelling because it provides the only explicit text that addresses each and every disputed element of the Asserted Claims. As Defendants point out, the Court found in ruling on the parties' motions for summary judgment that there was nothing in the labelling that explicitly told doctors to prescribe the drugs in an infringing way. (ECF No. 373 at 142.) But the Court finds—after receiving the benefit of the testimony and evidence presented at Trial—that the Clinical Studies section of the labelling recommends or encourages doctors to prescribe the applicable drug in a way that would, on average, infringe the Asserted Claims.[18] Finding otherwise would essentially require finding that doctors would not read the Clinical Studies section of Defendants' proposed labels. Such a finding would be contrary to medical practice, and contrary to the evidence presented at Trial. Moreover, there is explicit textual support for Plaintiffs' inducement theory in the Clinical Studies section of the labelling for all Asserted Claims—that a doctor would understand to suggest she should prescribe the drugs in an infringing way.

Defendants do not dispute that their proposed labelling will induce infringement of many common elements of the Asserted Claims. (ECF No. 324 at 26-28 (listing several undisputed elements of the Asserted Claims).) Instead, Defendants divide their induced infringement arguments into three parts regarding: (1) the limitation present in all Asserted

[17]The Court refers interchangeably to Plaintiffs' Vascepa labels and Defendants' proposed labels as they are materially the same for purposes of this analysis.

[18]As explained *supra*, other sections of the labelling also provide support for the Court's findings. The Court highlights the Clinical Studies section of the label here because it is pertinent to all Asserted Claims.

claims that the drug must be administered for at least 12 weeks; (2) the limitations present in most Asserted Claims that the drug either reduce TG levels by certain percentages, not increase LDL-C levels, or reduce Apo B levels (the "Other Health Benefits" claims); and (3) the limitations that exclude co-administration of the drug with a with another lipid altering drug such as a statin (the "Excluding a Statin" claims). (ECF No. 378 at 12-19, 32-33, 36-37.) The Court addresses each of these arguments in turn.

a) 12 Week Limitation

First, the evidence at Trial showed that, based on the proposed labelling, Defendants' ANDA Products will be prescribed for more than 12 weeks a sufficient percentage of the time for the Court to conclude Defendants will induce infringement of this claim limitation common to all Asserted Claims. A number of factors weigh in favor of this finding. To start, both Plaintiffs' and Defendants' experts testified that the indication and usage section of the proposed labels is directed to reducing TG levels below 500 mg/dL and then maintaining that reduction—suggesting that the applicable drugs will be prescribed long term. (*Compare* ECF No. 366 at 331:18-20, 364:19-365:18, 367:11-368:20, 536:22-537:15 (Plaintiffs' expert Dr. Budoff testifying as such) *with* ECF No. 367 at 672:11-675:2 (Defendants' expert Dr. Sheinberg conceding he would normally try to reduce TG levels and then maintain that reduction); *see also* ECF No. 368 at 1210:5-8 (Defendants' expert Dr. Fischer agreeing that, in many patients, "the indication is to reduce below 500 and to maintain that reduction below 500[.]").) Were a treating physician to stop therapy once TG levels had been reduced below 500, "in most cases [the TG levels] will go back up[.]" (ECF No. 366 at 378:21-379:2; *see also* 536:22-537:5.) That also supports Plaintiffs' view that the drug will often be prescribed for long-term treatment. So too do the prescribing practices of experts on both sides, who testified that they generally prescribe either four or twelve months of Vascepa at a time. (ECF Nos. 367 at 391:2-8, 393:10-21, 367 at 663:2-19.)

Trial testimony further established that severe hypertriglyceridemia generally has a genetic component, meaning that it is usually a chronic condition requiring long-term

treatment. (ECF No. 366 at 367:23-25, 373:12-389:25 (discussing various trial exhibits that support this view, and offering his own testimony to that effect).) And even Defendant's expert Dr. Sheinberg agreed that "sometimes severe hypertriglyceridemia is a chronic condition that requires indefinite drug treatment," even if his estimate of the percentage of chronic cases is lower than that of the other witnesses. (ECF No. 367 at 696:16-19.) Thus, there is no real dispute that severe hypertriglyceridemia is a chronic condition requiring long-term treatment at least some of the time. Conversely, there is also no real dispute that severe hypertriglyceridemia can be an acute condition some of the time, where a person experiences, for example, a spike in TG levels above 500 after, say, a bout of binge drinking. (ECF No. 366 at 450:12-15 ("severe hypertriglyceridemia can be an acute phenomenon[.]").) But overall, the Court finds Plaintiffs' expert Dr. Budoff's testimony to the effect that it is generally a chronic condition caused by genetics more persuasive. The Court therefore finds that severe hypertriglyceridemia is generally a chronic condition requiring long-term treatment. Prescribing doctors would bring that understanding to bear when they read Defendants' proposed labelling lacking an explicit duration of treatment—and most of them would prescribe Defendants' proposed ANDA Products for more than 12 weeks.

Moreover, the Clinical Studies section of Defendants' proposed labelling points towards the Court's finding that most doctors would prescribe Defendants' proposed ANDA Products for more than 12 weeks. Specifically, the Clinical Studies section of Defendants' labels, like Vascepa's label, reports the results of the MARINE study, which established the effectiveness of EPA 4 g per day in treating patients with severe hypertriglyceridemia. In describing the important details of the study, this section of the labeling expressly states that patients were administered icosapent ethyl 4 g per day "for 12 weeks." (Ex. 1186 at 11.) And as Defendants' regulatory expert Mr. Mathers conceded, Defendants' proposed labeling reports the treatment effects only at 12 weeks, not earlier, and thus reflects approval for reducing TGs below 500 mg/dL and maintaining that reduction through 12 weeks. (Mathers Dep. Tr. 97:2-16.) The fact that the Clinical Studies

section describes a 12 week trial suggests to prescribing doctors that they should "try to follow the prescribing information, and if the prescribing information was done at 12 weeks, then that informs the physician, that instructs the physician that you should wait 12 weeks to reassess lipids to see what the full effect of your treatment is, because [clinicians'] goal when putting [patients] on Vascepa is to achieve the results in Table 2." (ECF No. 366 at 372:3-12.") The labels therefore encourage, recommend, promote, or suggest that clinicians should administer Defendants' ANDA Products for at least 12 weeks to achieve the treatment effects reported in the labeling. (*See id.* at 372:16-374:5 ("[T]he only way I can compare my patient to the label and what's being encouraged is to follow the instructions that are given, and the instructions here are to treat for 12 weeks.").)

b) Other Health Benefits Claims

Defendants' narrower noninfringement argument is directed at the Other Health Benefits claims that require the claimed methods either reduce TG levels by certain percentages, not increase LDL-C levels, or reduce Apo B levels. (ECF No. 378 at 36-37.) But the Court finds Defendants' argument unpersuasive. As discussed above, the Court finds that a doctor would read and understand the Clinical Studies section of the labelling before she prescribed Defendants' ANDA Products because it is vital to understanding the effects of the applicable drug. (*See* ECF No. 367 at 665:1-13.) The Clinical Studies section of the labelling describes how the average patient enrolled in the MARINE study received the benefits described in the Other Health Benefits claims. A doctor would read these results as reported in the Clinical Studies section of the labelling as specifically encouraging infringement of the Other Health Benefits Claims.

Moving on to focus on the specific claim limitations within the Other Health Benefits Claims, Defendants' proposed ANDA labels specifically suggest to doctors that their ANDA Products will decrease TG levels without raising LDL-C levels. Not only does the Clinical Studies section report that patients experienced a 5% reduction in LDL-C compared to baseline and a 2% reduction in LDL-C compared to placebo, the Clinical Studies section also states that "[t]he reduction in TG [triglycerides] observed with

icosapent ethyl was not associated with elevations in LDL-C levels relative to placebo." (Ex. 1186 at 11; *see also* ECF No. 366 at 405:5-406:7.) Defendants' proposed labeling will thus inform prescribers that the drug is safe and effective for administration to patients with severe hypertriglyceridemia to reduce TGs without raising LDL-C. Indeed, Vascepa's ability to reduce TGs without raising LDL-C, as depicted in the Clinical Studies section, is a primary reason clinicians choose to prescribe Vascepa over other available medications. (ECF No. 366 at 406:7-407:6.) The Clinical Studies section of the labelling therefore suggests to doctors that they can prescribe Defendants' ANDA Products to lower TG levels without also raising LDL-C levels.[19] For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—"without substantially increasing LDL-C" as required, for example, by Claim 1 of the '728 patent.

Defendants' proposed ANDA labels also suggest to treating clinicians that they can expect a decrease in Apo B levels when they prescribe Defendants' ANDA Products. Similar to the analysis above concerning LDL-C, Defendants will induce infringement of the limitations concerning Apo B because clinicians will read Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to reduce TGs in severely hypertriglyceridemic patients and in conjunction with the TG reduction, "effect a statistically significant reduction . . . in apolipoprotein B." (ECF No. 366 at 427:9-19; *see also* ECF No. 369 at 1407:11-15.) Here, too, the Clinical Studies section of the labeling reports the statistically significant decrease in Apo B resulting from administration of Vascepa in Table 2 and then calls out in text below that

[19]Moreover, the Warnings and Precautions section in Defendants' labeling, like the same section in Vascepa's labeling, omits any warning that patients' LDL-C levels may rise as a result of treatment. (Ex. 1186 at 2-3.) The absence of a warning would be conspicuous to clinicians because the prescribing information for Lovaza and several fibrates contain such a warning. (ECF No. 366 at 407:17-25.) And physicians who treat patients with severe hypertriglyceridemia would be intimately familiar with the effects of other available drugs (niacin, fibrates, and Lovaza). (ECF No. 367 at 659:11-18.) The lack of a warning about LCL-C increases in Defendants' labeling is thus a further suggestion to doctors that Defendants' ANDA Products will decrease TG levels without increasing LDL-C levels.

the drug reduced both median TG and Apo B. (Ex. 1186 at 11; *see also* ECF No. 366 at 427:9-22.) The labeling thus conveys to physicians both the clinical significance of the drugs' effect on Apo B and the fact that such a reduction will generally occur in their patients in clinical practice. (ECF No. 366 at 427:15-428:5; *see also* ECF No. 369 at 1408:19-22 (testifying that FDA "interpreted this information and it called out that decrease. And so FDA approved this label, it approved this drug for the treatment of hypertriglyceridemia while reducing apo B"); Mathers Dep. Tr. 134:10-22 (stating that the Clinical Studies section of the labeling identifies Apo B among the "relevant parameters to measure on a routine basis and to monitor"). By instructing clinicians that 4 g per day of icosapent ethyl has been shown to cause a statistically significant reduction in TGs and Apo B when administered to adult patients with severe hypertriglyceridemia, the Clinical Studies section of Defendants' labeling encourages, recommends, promotes, or suggests that clinicians administer Defendants' ANDA Products with the intent to effect a statistically significant reduction in TGs while having the additional beneficial effect of a statistically significant reduction in Apo B. For these reasons, based on the instructions in Defendants' proposed labeling, Defendants' intend their ANDA Products to be used—and in clinical practice they will be used—"to effect a statistically significant reduction . . . in apolipoprotein B" as required by Claim 14 of the '715 patent. (Ex. 22 at 22, Claim 14.)

Defendants' proposed ANDA labels also suggest to doctors that they can expect certain reductions in TG levels by prescribing those ANDA Products, as required by certain other Asserted Claims. Defendants will therefore induce infringement of these limitations because clinicians will read the Clinical Studies section of Defendants' labeling as encouraging, recommending, promoting, or suggesting administration of Defendants' ANDA Products to achieve, on average, the percentage TG reductions described in certain Asserted Claims. Table 2 in the Clinical Studies section of Defendants' proposed labeling, like the same table in Vascepa's labeling, reports that, when administered for 12 weeks to patients with severe hypertriglyceridemia, EPA 4 g per day caused a median 27% reduction in triglycerides from baseline and a median 33% reduction in triglycerides

compared to placebo. (Ex. 1186 at 11; *see also* ECF No. 366 at 433:23-434:3.) For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice they will be used—to reduce TG levels by the percentages required by Claim 4 of the '560 Patent and Claim 17 of the '560 Patent. (ECF No. 366 at 433:16-435:2, 435:6-436:20.)

c) Excluding a Statin Claims

Defendants' narrowest noninfringement argument is directed at the Excluding a Statin claims. (ECF No. 378 at 32-33.) The Court is also unpersuaded by this argument. To the contrary, the labels of Defendants' proposed ANDA Products suggest to a doctor that the drugs could be used with or without a statin or other lipid-lowering drug.

The Excluding a Statin limitation requires administration of the claimed pharmaceutical composition to a patient "who does not receive concurrent lipid altering therapy." (Ex. 21 at 21-22 Claims 1,16; *see also* Ex. 22 at 22, Claim 14 ("who does not receive a concurrent lipid altering therapy").) The Court construed the term "concurrent lipid altering therapy" to mean "a medication to alter lipid levels in a subject whereby the medication is administered concurrently / concomitantly with the administration of a pharmaceutical composition comprising ethyl eicosapentaenoate." (ECF No. 135 at 5-7.) Statins are an example of a "medication to alter lipid levels." (ECF No. 366 at 412:1-6, 414:1-20 (identifying statins as concurrent lipid altering therapies).) Based on the Court's construction, a clinician who administers Defendants' ANDA Products to a patient who is not on another lipid altering medication (*e.g.*, a statin) will directly infringe this limitation.

There is text in several places on Defendants' proposed labelling that would suggest to doctors Defendants' proposed ANDA Products could be administered without a concurrent lipid altering therapy. First, the Indications and Usage section does not contain any instructions that Defendants' ANDA Products must be administered with a lipid-altering drug, though FDA regulations would have required instructions to that effect were that the case. (ECF No. 366 at 410:11-25 (testifying that the label does not require concurrent lipid-altering therapy); Ex. 573 at 7, 12 (stating that coadministration should be

listed were it a requirement).) Second, and similarly, the Dosage and Administration section of the labelling would have had to mention it, but did not. (Ex. 572 at 8 (stating any concomitant medications should be listed in this section); *see also* Ex. 1186 at 2 (labelling, which does not include such a restriction); ECF No. 369 at 1355:3-6 (explaining that the labelling does not mention such a restriction).) Third, the Clinical Studies section of the labelling indicates that only 25% of the MARINE study participants were on a concomitant lipid-altering therapy. (Ex. 1186 at 11.) Clinicians appreciate from this clinical study description that the remaining 75% of patients in the study described in the Clinical Studies section were not on concurrent lipid altering therapy (*e.g.*, statins). (ECF No. 369 at 1413:8-18; *see also* Mathers Dep. Tr. at 68:1-5, 68:7-15.) For these reasons, based on the instructions in Defendants' proposed labeling, Defendants intend their ANDA Products to be used—and in clinical practice will be used—by patients who "do[] not receive concurrent lipid altering therapy" as required by certain claims of the Asserted Patents. (ECF No. 366 at 409:7-415:11 (discussing the monotherapy limitation of the '728 patent).)

The Court therefore finds that the labels of Defendants' proposed ANDA Products encourage, recommend, promote, or suggest that clinicians prescribe those products in a way that infringes all of the Asserted Claims.

Defendants' arguments to the contrary are unavailing. First, as Defendants continue to argue that their proposed ANDA Products' substantial noninfringing uses should change the Court's analysis in various ways (ECF No. 378 at 12-13), the Court reiterates that "contributory infringement can turn on whether there are substantial non-infringing uses, while inducement does not." (ECF No. 278 at 8.) *See also Sanofi v. Watson Labs. Inc.*, 875 F.3d 636, 646 (Fed. Cir. 2017) ("[T]here is no legal or logical basis for the suggested limitation on inducement."). Second, and relatedly, Defendants argue that induced infringement cannot be inferred under these circumstances—that inducement cannot be found without specific instructions in the label. (ECF No. 378 at 12.) But the Court has done no such thing. The Court is not inferring infringement without looking at the content of the label. Rather, and as explained above, the Court is reading primarily the

Clinical Studies section of the label as trial testimony established a doctor would read it. For that same reason, the caselaw Defendants rely on, *Grunenthal* and *Horizon*, is distinguishable. (ECF No. 378 at 14.) Unlike in those cases, there is support in the text of Defendants' proposed ANDA labels for the plausible interpretation of those labels, supported by expert testimony, that the Court finds encourages infringement here. Third, to the extent the Court has not made it clear above, the Court finds the evidence presented at Trial shows that severe hypertriglyceridemia is a chronic condition necessitating indefinite treatment most of the time, or at least enough of the time for the Court to properly find inducement here. Thus, the Court rejects Defendants' argument that they do not infringe the 12 week limitation of the Asserted Claims because severe hypertriglyceridemia is not a chronic condition. (ECF No. 378 at 8.)

In sum, the Court finds that Defendants' labelling will induce infringement of all Asserted Claims. However, as further explained below, the Court also finds that All Asserted claims are invalid as obvious in light of the prior art.

B. Obviousness

1. Legal Standards

Under 35 U.S.C. § 103, a patent is invalid as obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." Whether a patent claim is obvious is ultimately a question of law based on four underlying factual determinations: (1) "the scope and content of the prior art"; (2) "the level of ordinary skill in the pertinent art"; (3) the "differences between the prior art and the claims at issue"; and (4) "[s]uch secondary considerations as commercial success, long-felt but unsolved needs, [and the] failure of others . . . ." *Graham*, 383 U.S. at 17.

"A party seeking to invalidate a patent based on obviousness must demonstrate 'by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the

skilled artisan would have had a reasonable expectation of success in doing so.'" *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)). Defendants, as the accused infringers, bear the ultimate burden of proving, by clear and convincing evidence, that the Asserted Claims are invalid. *See Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011). That said, where "the PTO did not have all material facts before it, its considered judgment may lose significant force," and courts should "consider that fact when determining whether an invalidity defense has been proved by clear and convincing evidence." *Id.* at 111; *see also Syntex (U.S.A.) LLC v. Apotex*, Inc., 407 F.3d 1371, 1379 (Fed. Cir. 2005) (finding reversible error where "district court failed to appreciate that the prosecution history of the relevant patents, while not establishing inequitable conduct, casts some doubt on the final examiner's conclusion that the claimed [invention] produces unexpected results sufficient to overcome a prima facie case of obviousness.").

a) Motivation to Combine

Federal Circuit "case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention." *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (internal quotation omitted). "The question is whether there is something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination, not whether there is something in the prior art as a whole to suggest that the combination is the most desirable combination available." *Id.* (citation omitted). "[T]here is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention." *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 (Fed. Cir. 1997).

b) Reasonable Expectation of Success

For the reasonable expectation of success component, although the definition is "somewhat vague, [Federal Circuit] case law makes clear that it does not require a certainty of success." *Medichem, SA v. Rolabo, SL*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

"Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (citation omitted). Difficulties in receiving FDA approval "are not particularly probative with respect to obviousness" because "[t]here is no requirement that one of ordinary skill have a reasonable expectation of success in developing" the FDA approved drug. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). Rather, "the person of ordinary skill need only have a reasonable expectation of success of developing the claimed invention." *Id.*

c) Secondary Considerations

Part of the obviousness inquiry also considers whether objective indicia of non-obviousness support the Asserted Claims. "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17-18; *see also In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (explaining that objective evidence of nonobviousness may include copying, long felt but unsolved need, failure of others, commercial success, unexpected results created by the claimed invention, unexpected properties of the claimed invention, licenses showing industry respect for the invention, and skepticism of skilled artisans). "Secondary considerations help inoculate the obviousness analysis against hindsight." *ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018) (quotation omitted). However, "a strong showing of obviousness may stand even in the face of considerable evidence of secondary considerations." *Id.* at 1374 (quotation omitted).

2. Discussion

The Court first discusses Defendants' *prima facie* obviousness case, which the Court finds Defendants supported with clear and convincing evidence of obviousness at Trial, and then discusses each of Plaintiffs' proffered objective indicia of nonobviousness. The Court will go on to explain why the Court does not find that Plaintiffs' proffered evidence of secondary considerations saves the Asserted Claims.

a) Prima Facie Obviousness

As an initial matter, the Court is persuaded that Defendants presented clear and convincing evidence at Trial that all Asserted Claims are invalid as obvious. The heart of Defendants' persuasive obviousness argument is that the Lovaza PDR covers many of the limitations of the Asserted Claims, and making the obvious substitution of only EPA instead of a mixture of EPA and DHA renders most limitations of the Asserted Claims obvious. The result of this obvious substitution, obtained by combining the Lovaza PDR and Mori, is the method recited in all Asserted Claims.

Although Plaintiffs dispute that the claimed method was obvious, they concede a number of Defendants' key premises. For instance, there is no dispute that the only difference between the method in the Lovaza PDR and the method in the asserted claims is that Lovaza contained a mixture of EPA and DHA, instead of purified EPA. (ECF No. 367 at 762:6-14; *see also* ECF No. 371 at 1821:5-1823:1.) Nor is there any dispute that the increases in LDL-C caused by Lovaza were known, and that "a skilled artisan would have been motivated to avoid LDL-C increases when treating patients with severe hypertriglyceridemia." (ECF No. 371 at 1822:8-11.) Moreover, while "many patients who took Lovaza were also given a statin to address the LDL-C increases," Plaintiffs' expert Dr. Toth agreed that since "those patients would have to take two pills, the Lovaza and a statin," "a skilled artisan would have been motivated to develop a single pill that treats severe hypertriglyceridemia without LDL-C increases." (*Id.* at 1822:12-21; *see also* ECF No. 367 at 813:8-814:2.)

Further, the Court finds that a skilled artisan would have wanted to know which active ingredient in Lovaza—EPA or DHA—was responsible for the LDL-C increase (if not both), and that Mori addressed this exact issue. Indeed, Dr. Toth did not dispute that "a skilled artisan seeing that there's DHA and EPA in Lovaza, and seeing a side effect, would at least consider whether the side effect could be associated with only DHA or only EPA." (ECF No. 371 at 1787:6-10.) Nor did he dispute that "Mori found that the increase of LDL-C with DHA was statistically significant and the increase with EPA was not." (*Id.* at

1788:18-25.) While Dr. Toth disputed other aspects of Defendants' obviousness defense (addressed further below), the key premises that he conceded lead directly to the motivation to combine and reasonable expectation of success that Defendants have asserted.

In addition to the claimed method of treatment, and as discussed above as to infringement, all but one asserted claim (claim 1 of the '929 patent) requires certain effects on a patient's lipids—a minimum reduction in triglycerides (*e.g.*, at least about 20%); no increase in LDL-C; or a reduction in Apo B (again, these are the Other Health Benefits Claims). As discussed in the findings of fact above, the prior art showed that purified EPA produced each of the claimed effects in clinical studies. In particular, Mori and Hayashi disclosed that EPA reduced triglycerides by at least about 20%; Mori, Hayashi, and Kurabayashi disclosed that EPA did not increase LDL-C; and Kurabayashi disclosed that EPA reduced Apo B.

One asserted claim (claim 16 of the '728 patent) further requires that the EPA product used to treat the patient contains no more than 0.6% of any other fatty acid. There is no dispute that this level of purity was disclosed and rendered obvious at least by WO '900,[20] which taught a process for producing "99.9% EPA" with "less than 0.1% of DHA." (Ex. 1525 at 17.)

Critically, in view of the claim language, obviousness is proven as long as there was a reasonable expectation that 4 g/day of 96% purified EPA would achieve the claimed effects (*i.e.*, not cause an LDL-C increase) in patients with triglycerides of exactly 500 mg/dL. "It is a long-established rule that claims which are broad enough to read on obvious subject matter are unpatentable even though they also read on nonobvious subject matter." *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1281 (Fed. Cir. 2015) (quotation omitted). Thus, to prove obviousness, Defendants do not need to prove that a skilled

[20]The parties stipulated to the fact that this reference is prior art. (ECF No. 324 at 9.)

artisan would have reasonably expected success in achieving the claimed effects in patients with triglycerides above 500 mg/dL, much less substantially above that level.

Also, this case is unlike many other obviousness cases because, when the Patent Office issued the patents-in-suit, it maintained its finding from earlier rejections that the prior art rendered all of the claims prima facie obvious. (Ex. 1521 at 1822-35, *see also id.* at 1830-31.) As the examiner explained, "it was concluded that it will be obvious to treat patients having triglycerides above 500 mg/dL with 96% pure ethyl-EPA." (*Id.* at 1830.) The examiner thus agreed with Defendants' view that the prior art would have motivated a skilled artisan to practice the asserted claims with a reasonable expectation of success (issuing the patents based solely on secondary considerations). (ECF No. 371 at 1804:22-1806:1; *see also* ECF No. 331 at 152 (noting in Plaintiffs' proposed findings of fact that "the Examiner concluded that it would be prima facie obvious to treat patients having TG above 500 mg/dl with 96% pure ethyl-EPA").)

The Court therefore finds that Defendants established by clear and convincing evidence at Trial that all Asserted Claims are *prima facie* obvious. Plaintiffs arguments to the contrary are unavailing. Many of Plaintiffs' arguments depend on the premise that POSAs as of March 2008 would not have expected that using a composition of purified EPA would not increase LCL-C levels. (ECF No. 379 at 22-23.) But this premise is not supported by the evidence. To explain, Plaintiffs primarily point to testimony from Dr. Toth to support this premise. But there are at least three issues with Dr. Toth's testimony. First, he agreed under questioning that, as of "March 2008 [. . .] the prior art reflect[ed] that all these treatments increased LDL-C in patients with very high triglycerides." (ECF No. 370 at 1574:1-1575:1.) But that cannot be correct, because Mori taught that EPA did not increase LDL-C levels like DHA did. (Ex. 1538 at 3.) Second, Dr. Toth testified that von Schacky contributed to his view that all TG-lowering therapies increase LDL-C levels. (ECF No. 370 at 1697:9-1703:7.) But as Defendants point out (ECF No. 378 at 26), von Schacky did not correctly summarize Mori. Specifically, von Schacky, citing Mori, wrote, "In more recent comparative studies, no effects of either EPA or DHA were seen on total

cholesterol, HDL, or LDL levels." (Ex. 1605 at 5.) But even Dr. Toth agreed on cross-examination that is not what Mori said. (ECF No. 371 at 1847:8-17.) Mori actually found that LDL-C increased with DHA, but not EPA. (Ex. 1538 at 3.) Third, part of Dr. Toth's opinion, and Plaintiffs' argument, is based on the Carlson reference from 1977. (ECF No. 377 at 43-44 (citing ECF No. 370 at 1577:22-25 and Ex. 1026.).) The Court is unpersuaded that an article from 1977 reflects the knowledge of a POSA in 2008. Thus, Plaintiffs' argument, in part based on Dr. Toth's testimony—that a POSA would have thought that both DHA and EPA would cause an increase in LDL-C in March 2008—lacks evidentiary support. The Court accordingly rejects this argument.

Moreover, Plaintiffs' arguments also depend on another factual premise that lacks evidentiary support—that patients with TG levels above 500 mg/dL respond differently to TG-lowering therapy than patients with TG levels below 500 mg/dL. (ECF No. 379 at 23-24.) But even if Mori and other studies on patients with lower TGs did not provide "conclusive proof" of EPA's effects, they were enough to form "a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331. Indeed, Dr. Toth conceded that POSAs could rely on data in patients with triglycerides below 500 mg/dL to make reasonable predictions about how patients above that threshold would respond. As he admitted, "a skilled artisan would know that a drug that reduces triglycerides in a patient at 400, is very likely to also reduce triglycerides in a patient at 600." (ECF No. 371 at 1860:8-11.) Thus, the Court finds that a POSA "would have reasonably expected purified EPA to reduce triglyceride levels above 500," even without data confirming that result. (*Id.* at 1860:12-15.)

There was no reason to expect differently for LDL-C. Dr. Toth cited no evidence that the 500 mg/dL threshold reflects any difference in how patients metabolize drugs, or any relationship between that specific threshold and LDL-C. As he admitted, "[t]he 500 threshold was not set because above 500 you are expected to have a greater increase in LDL-C in response to a drug." (*Id.* at 1860:3-7.) Instead, all experts agreed that the threshold simply represents a marker for the risk of pancreatitis, which has nothing to do

with LDL-C levels. (ECF No. 371 at 1859:3-13; *see also* Bays Dep. Tr. at 143:9-11, 143:13-19.) In Dr. Heinecke's words, there is no "magical mechanistic difference" between having triglycerides of 400, 500, or 600 mg/dL. (ECF No. 367 at 796:5-20.) A skilled artisan would understand that, regardless of a patient's baseline triglycerides, "the qualitative effects of medications . . . tend to be the same." (*Id.* at 797:16-18.)

Finally, Plaintiffs try to discredit Mori by pointing to von Schacky. (ECF No. 379 at 24.) But the Court credits Mori over von Schacky, because, as described above, von Schacky incorrectly summarized Mori, and is therefore not credible. In sum, having found that Defendants met their clear and convincing burden to prove their *prima facie* obviousness case at trial, the Court turns to consideration of Plaintiffs' proffered secondary considerations.

b) Secondary Considerations

"[E]vidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). The Court therefore addresses each of the secondary considerations proffered by Plaintiffs. Plaintiffs specifically point to unexpected benefits, satisfaction of long-felt but unmet need, skepticism, praise, and commercial success. (ECF No. 377 at 10.) But before the Court addresses each of these secondary considerations, the Court addresses Defendants' challenge to the nexus between the REDUCE-IT clinical trial results and the Asserted Claims—which the Court finds persuasive.

i. REDUCE-IT

Plaintiffs rely on the results of the REDUCE-IT clinical trial to support several of their secondary considerations arguments. (ECF No. 379 at 35-38.) However, Defendants counter that, as a matter of law, the Court should not consider the results of the REDUCE-IT study in analyzing Plaintiffs' proffered secondary considerations because REDUCE-IT lacks a sufficient nexus to the Asserted Claims. (ECF No. 378 at 30-32.) The Court agrees with Defendants.

Regardless of whether a presumption of nexus applies here,[21] there is no nexus between REDUCE-IT and the Asserted Claims. "It is the established rule that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *Allergan*, 754 F.3d at 965 (quotation omitted; reversing judgment of nonobviousness). "Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (emphasis omitted). For multiple reasons, Plaintiffs' evidence regarding REDUCE-IT does not satisfy these requirements.

First, REDUCE-IT lacks a nexus to the claimed use of Vascepa without a statin. As Dr. Toth admitted, "none [of] the asserted claims require a statin." (ECF No. 371 at 1896:23-24.) In fact, three claims expressly require treating a patient "who does not receive concurrent lipid altering therapy," and thus preclude using a statin. (Ex. 1500 ('728 patent claims 1 and 16); Ex. 1502 ('715 patent claim 14).) In contrast, "all the patients in REDUCE-IT were taking statins"—"100 percent." (ECF No. 371 at 1896:15-19; *see also* Ex. 1641 at 2.) In fact, there is no dispute that a statin must be administered to reduce cardiovascular risk with Vascepa. As Dr. Toth testified, "it would have been unethical to have just a Vascepa monotherapy arm [in REDUCE-IT]. The FDA would never allow it because statin therapy is the standard of care." (ECF No. 371 at 1897:5-10.) This is reflected in the REDUCE-IT indication, which makes clear that Vascepa reduces cardiovascular risk only "as an adjunct to maximally tolerated statin therapy." (Ex. 2248 at 2.)

The REDUCE-IT results are therefore not "commensurate in scope with the claims." *Allergan*, 754 F.3d at 965. For the three claims that exclude statins, the benefits of

[21]The parties dispute whether a presumption of nexus applies (ECF Nos. 378 at 30-31, 379 at 35), but the Court need not—and does not—resolve that dispute because the Court finds, as explained *infra*, that there is an insufficient nexus between REDUCE-IT and the Asserted Claims.

REDUCE-IT are entirely outside the scope of the claims. But even for the claims that are silent on statin use, there is no dispute that Vascepa can be, and often is, used without a statin in accordance with the claimed method. As Dr. Toth agreed, only "25 percent of the patients in MARINE were taking statins." (ECF No. 371 at 1896:20-22.) At most, therefore, the REDUCE-IT results could only be relevant to that subset of patients. But the Asserted Claims are much broader—they include the 75% of patients in MARINE who took Vascepa without a statin. Because the REDUCE-IT results are "not commensurate with the full scope of the patent's claims," they "lack[] a nexus with the scope of the [asserted] patent[s'] claimed invention." *Allergan*, 754 F.3d at 965.

Put differently, the benefits in REDUCE-IT "actually result[ed] from something other than" the claimed invention, which at least allows using Vascepa without a statin. *In re Huai-Hung Kao*, 639 F.3d at 1068. Instead, the benefits resulted from a different invention—one claimed in Plaintiffs' unasserted patents—which requires using a statin. (Ex. 2001 at 1, 52-53.) REDUCE-IT thus lacks a nexus to the Asserted Claims. (ECF No. 367 at 821:2-18.)

Second, REDUCE-IT lacks a nexus to the claimed use of EPA to reduce triglycerides. As Dr. Toth conceded, "none of the patent claims at issue in this case have a limitation with regard to reducing cardiovascular risk." (ECF No. 371 at 1894:15-18.) Instead, all asserted claims are directed to "[a] method of reducing triglycerides." The benefits in REDUCE-IT, however, were unrelated to reducing triglycerides. According to the REDUCE-IT publication (the Bhatt Article), "the significantly lower risk of major adverse cardiovascular events with icosapent ethyl than with placebo appeared to occur irrespective of the attained triglyceride level at 1 year (≥150 or suggest that at least some of the effect of icosapent ethyl that resulted in a lower risk of ischemic events than that with placebo may be explained by metabolic effects other than a reduction of triglyceride levels." (Ex. 1641 at 10.) In other words, the REDUCE-IT benefits "actually result[ed] from something other than" the claimed method of reducing triglycerides, which precludes any finding of nexus. *In re Huai-Hung Kao*, 639 F.3d at 1068. (*See also* ECF Nos. 367 at 816:8-

817:12, 368 at 1035:4-1037:2.) On cross-examination, Plaintiffs argued that "the Bhatt [A]rticle doesn't rule out TG lowering as responsible for at least part of the CV benefit." (ECF No. 368 at 1119:11-14.) But on the contrary, the evidence of record, including the Bhatt Article, suggests the opposite. Thus, there is no basis to conclude that the REDUCE-IT results have a nexus to the claimed method of reducing triglycerides.

Third, REDUCE-IT lacks a nexus to avoiding an increase in LDL-C, which is a limitation of all but two Asserted Claims, and is the purported discovery that allegedly distinguishes the Asserted Claims from the prior art. According to the Bhatt Article, the REDUCE-IT investigators "found no substantial difference in the benefit of icosapent ethyl as compared with placebo with respect to the primary end point according to whether the patients who received placebo had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels." (Ex. 1641 at 7.) Thus, the REDUCE-IT benefits "actually result[ed] from something other than" the claimed method of avoiding an increase in LDL-C, as required by eight of the asserted claims. (ECF No. 367 at 820:13-821:1. *See also In re Huai-Hung Kao*, 639 F.3d at 1068.

Fourth, the REDUCE-IT results are not commensurate in scope with the Asserted Claims because the results were limited to patients with multiple cardiovascular risk factors that the asserted claims do not require. As explained in the Bhatt Article, REDUCE-IT was limited to patients who "were 45 years of age or older and had established cardiovascular disease or were 50 years of age or older and had diabetes mellitus and at least one additional risk factor." (Ex. 1641 at 2.) Likewise, the REDUCE-IT indication is limited to patients with "established cardiovascular disease or diabetes mellitus and 2 or more additional risk factors for cardiovascular disease." (Ex. 2248 at 2.) By contrast, the Asserted Claims do not contain any of these limitations. As Dr. Toth admitted, "aside from severe high triglycerides, there's no other risk factor[] required by the patents related to cardiovascular issues." (ECF No. 371 at 1894:22-25.) For example, none of the Asserted Claims are limited to patients with diabetes. (ECF Nos. 367 at 826:10-12, 368 at 1093:21-22.) Moreover, there is no dispute that many patients with severe hypertriglyceridemia do

not have risk factors such as diabetes. For example, in MARINE, only 28% of patients were diabetic. (Ex.1741 at 2; *see also* ECF No. 367 at 825:22-826:9.) The Asserted Claims cover the treatment of the remaining patients who were not diabetic, as well as patients who more generally do not have two or more cardiovascular risk factors. Because the REDUCE-IT results are limited to patients with such risk factors, they are "not commensurate with the full scope of the patent's claims." *Allergan*, 754 F.3d at 965.

Fifth, REDUCE-IT lacks a nexus to the limitation in all Asserted Claims that patients must have TG levels of at least 500 mg/dL. As Dr. Toth admitted, "REDUCE-IT focused on patients with triglycerides below 500." (ECF No. 371 at 1894:12-14.) According to the Bhatt Article, "[e]ligible patients had a fasting triglyceride level of 150 to 499 mg per deciliter," which means that patients with triglyceride of at least 500 mg/dL were not eligible to participate. (Ex. 1641 at 2.) The benefits in REDUCE-IT thus "actually result[ed] from something other than" the claimed invention, which is limited to treating patients with triglycerides of at least 500 mg/dL, so "there is no nexus[.]" (ECF No. 367 at 818:12-819:16.) *See also In re Huai-Hung Kao*, 639 F.3d at 1068. Indeed, because REDUCE-IT focused on patients with triglycerides below 500 mg/dL, conducting REDUCE-IT did not even infringe the Asserted Claims. Moreover, in analogous circumstances, the Federal Circuit has held that evidence regarding products that are not covered by the asserted claims cannot be relevant to secondary considerations. The same principle applies to the method claims here—because the Asserted Claims do not cover the REDUCE-IT study, evidence regarding REDUCE-IT is irrelevant. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 n.42 (Fed. Cir. 1985) (stating if "products were not covered by the [asserted] patents, [ ] then the secondary considerations [based on those products] would not have had any relevance to the obviousness/nonobviousness determination"); *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 1366 (Fed. Cir. 2001) (holding that secondary considerations based on "copying Amazon's '1-Click®' feature is legally irrelevant unless the '1-Click®' feature is shown to be an embodiment of the claims").

Plaintiffs argue that some patients in REDUCE-IT developed higher triglyceride levels after they became eligible for the study, and thus the study did include a handful of patients with triglycerides of at least 500 mg/dL. (ECF No. 379 at 35 n.10.) But Plaintiffs' argument contradicts their position that Defendants' prior-art references are not relevant unless all patients in the study had triglycerides of at least 500 mg/dL. Plaintiffs cannot have it both ways. If studies in which no patients, or only a handful of patients, had triglycerides of at least 500 mg/dL are irrelevant, then so is REDUCE-IT.

In sum, for multiple independent reasons, the REDUCE-IT results are not commensurate in scope with, and did not actually result from practicing, any of the Asserted Claims. Thus, there is an insufficient nexus between REDUCE-IT and the Asserted Claims. As a result, evidence concerning REDUCE-IT is not relevant to determining whether the Asserted Claims are invalid as obvious.

ii. Unexpected Benefits

Plaintiffs also argue that the positive lipid effects recited in the Other Health Benefit claims are unexpected benefits that constitute another secondary consideration weighing in favor of nonobviousness. (ECF No. 377 at 252-257.) Defendants counter that these benefits were not unexpected because they were predicted by the relevant prior art. (ECF No. 378 at 29.) The Court agrees with Defendants.

As explained above as to Defendants' *prima facie* obviousness case, Mori found that EPA did not raise LDL-C levels, and Kurabayashi suggested that EPA reduced Apo B levels. (ECF No. 373 at 76-80, 246-47.) Further, while the Patent Office found that a decrease in Apo B was an unexpected benefit constituting a valid secondary consideration, the Patent Office's examiner did not consider Kurabayashi. (*Id.* at 246-47.) Where "the PTO did not have all material facts before it, its considered judgment may lose significant force[.]" *See i4i*, 564 U.S. at 95. Thus, the Court finds that the unexpected benefits secondary consideration does not weigh in favor of finding the Asserted Claims nonobvious.

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iii. Satisfaction of Long-Felt Need

Plaintiffs also argue that the Asserted Claims are not obvious because Vascepa satisfied long-felt needs—"as it is the first approved treatment that reduces TGs without raising LDL-C in patients with severe hypertriglyceridemia, and the first treatment for reducing TGs in severely hypertriglyceridemic patients that reduces cardiovascular risk on top of statin." (ECF No. 377 at 261.) Defendants counter that there was no long-felt need to reduce TGs without raising LDL-C because a patient could also be put on a statin to avoid the LDL-C increase. (ECF No. 378 at 29-30.) The Court agrees with Plaintiffs.

The Court is persuaded that there was a long-felt need for a drug like Vascepa that could reduce TG levels without raising LDL-C levels, primarily because both sides' experts testified that patients are more likely to comply with a prescribed treatment regime when they only have to take one pill, rather than two—and the Court relied on this evidence in finding a POSA would be motivated to combine the Lovaza PDR with the finding from Mori that EPA did not raise LDL-C levels.[22] (*See supra* Section IV.B.2(a).) It is better to take one pill than two if taking that one pill will give you all the same benefit. Moreover, there is no real dispute that some patients may not be able to tolerate statins. (ECF No. 367 at 660-61.) Thus, the Asserted Claims represent an improvement—albeit a prima facie obvious one—over the prior art. And this secondary consideration therefore weighs slightly in favor of finding the Asserted Claims nonobvious.

iv. Skepticism

Skepticism about an invention is evidence that an invention was not obvious. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Plaintiffs argue that this secondary consideration weighs in their favor because experts were skeptical that Vascepa could

[22]However, the Court notes that the Court does not credit the REDUCE-IT Indication as weighing in Plaintiffs' favor as to this factor because the Court has already found REDUCE-IT lacks the required nexus to the Asserted Claims *supra* in Section IV.B.2(b).i.

lower TG levels without also raising LDL-C levels.[23] (ECF No. 377 at 268.) Defendants counter that Plaintiffs did not present any expert testimony at Trial regarding skepticism, and only cite to the opinions of two experts retained by Plaintiffs to serve on an expert panel during Vascepa's development—and their opinions are irrelevant because Plaintiffs did not present any evidence these experts were aware of the prior art Defendants relied on in this case. (ECF No. 378 at 30.) The Court agrees with Defendants.

Plaintiffs' proffered evidence of skepticism is not inconsistent with Defendants' argument. Specifically, Plaintiffs point to notes taken by Ian Osterloh at Plaintiffs' expert meeting earlier on in the development of Vascepa and related deposition testimony, and specifically point to this note: "LDL-C is likely to go up as it does with virtually all tg-lowering therapies in this group of patients." (ECF No. 377 at 268 (citing Ex. 754 at 2).) But of course, the phrase 'virtually all' does not mean 'all,' and the Court agrees with Defendants that this view does not appear to account for Mori. And a skeptical statement is entitled to less weight if, as appears to be the case here, the person who made the statement was unaware of relevant prior art that would likely have made them less skeptical. *See PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1365 (Fed. Cir. 2007) (discounting testimony expressing surprise where "there was no indication that either [the declarant] or members of his research group were previously aware of the prior art references that laid the groundwork for the inventors' experiments."). In sum, the Court finds that the skepticism secondary consideration does not weigh in favor of finding the Asserted Claims nonobvious.

v. Praise

The Court found, as a factual matter *supra* in Section III.G.4(c), that Plaintiffs' proffered evidence of praise for Vascepa was more qualified and equivocal than Plaintiffs

[23]Plaintiffs also make skepticism arguments based on the REDUCE-IT Indication (ECF No. 377 at 268-69), but the Court does not consider those arguments because REDUCE-IT lacks the required nexus to the Asserted Claims, as explained *supra* in Section IV.B.2(b).i.

argued, and thus finds that the praise secondary consideration does not weigh in favor of finding the Asserted Claims nonobvious.

vi. Commercial Success

But the Court also found, as a factual matter *supra* in Section III.G.4(b), that Vascepa is a commercial success. This secondary consideration therefore weighs in favor of finding the Asserted Claims nonobvious.

vii. Weighing These Secondary Considerations

The Court thus finds that the satisfaction of long-felt need and commercial success secondary considerations weigh in Plaintiffs' favor, and the remaining secondary considerations weigh in Defendants' favor. More specifically, the Court finds that Vascepa is a commercial success even though it has not yet turned a profit, and that there was long felt need for a single pill that reduced TG levels without increasing LDL-C levels. However, these secondary considerations are outweighed by the fact that the Court found Plaintiffs' other proffered secondary considerations favor Defendants. Thus, at best, Plaintiffs have presented weak evidence of the existence of secondary considerations, which do not overcome the Court's finding that all Asserted Claims are *prima facie* obvious. *See, e.g.*, *ZUP*, 896 F.3d at 1373 (holding that "a strong showing of obviousness may stand even in the face of considerable evidence of secondary considerations").

For the reasons discussed above, in view of all four *Graham* factors (including alleged secondary considerations), Defendants have proven by clear and convincing evidence that all Asserted Claims are invalid as obvious under 35 U.S.C. § 103.

C. Remedies

Plaintiffs seek a permanent injunction that Defendants be prohibited from marketing their proposed ANDA Products until Plaintiffs' Asserted Patents expire, and that their ANDA applications similarly should not be made effective until Plaintiffs Asserted Patents expire. (ECF No. 377 at 300-01.) However, Plaintiffs are not entitled to these remedies because, while the Court found that Defendants' proposed ANDA Products will induce

infringement of the Asserted Claims, all of the Asserted Claims are invalid as obvious under 35 U.S.C. § 103.

V. CONCLUSION

The Court notes that the parties made arguments and cited to cases not discussed above. The Court has reviewed these arguments and cases, and has determined they do not materially affect the outcome of this case.

The Court finds that Defendants' proposed ANDA Products will induce infringement of the Asserted Claims, but all the Asserted Claims are invalid as obvious under 35 U.S.C. § 103. Thus, the Court finds in favor of Defendants on Plaintiff's remaining infringement claim, and in their favor on their counterclaims asserting the invalidity of the Asserted Claims under 35 U.S.C. § 103.

The Clerk of Court is ordered to enter judgment in favor of Defendants on Plaintiffs' claim and on Defendants' counterclaims, and close this case.

DATED THIS 30th day of March 2020.

MIRANDA M. DU
CHIEF UNITED STATES DISTRICT JUDGE