20-1723

United States Court of Appeals for the Federal Circuit

AMARIN PHARMA, INC. and AMARIN PHARMACEUTICALS IRELAND LIMITED,

Plaintiffs/Appellants,

v.

HIKMA PHARMACEUTICALS USA INC., HIKMA PHARMACEUTICALS INTERNATIONAL LIMITED, DR. REDDY'S LABORATORIES, INC. and DR. REDDY'S LABORATORIES, LTD.,

Defendants/Appellees,

APPEAL FROM THE U.S. DISTRICT COURT FOR THE DISTRICT OF NEVADA, IN CASE NO. 2:16-CV-02525-MMD, JUDGE MIRANDA M. DU

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May 12, 2020

CERTIFICATE OF INTEREST

Counsel for the Appellant, Amarin Pharma, Inc., and Amarin Pharmaceuticals Ireland Limited, certifies the following:

1. The full name of every party represented by me is: Amarin Pharma, Inc., and Amarin Pharmaceuticals Ireland Limited

2. The name of the real party in interest (please only include any real party in interest NOT identified in Question 3) represented by me is: Amarin Corporation plc

3. Parent corporations and publicly held companies that own 10% or more of stock in the party: Both Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited are wholly-owned subsidiaries of Amarin Corporation plc

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court (**and who have not or will not enter an appearance in this case**) are:

McDonald Carano LLP: Adam Hosmer-Henner; Chelsea Latino
Covington & Burling LLP: Einar Stole; Michael N. Kennedy; Megan P. Keane; Alaina M. Whitt; Han Park; Jordan L. Moran; Daniel J. Farnoly
Santoro Whitmire, Ltd.: Nicholas J. Santoro; Jason D. Smith

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will affect or be directly affected by this court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b): *Amarin Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, 2:18-cv-01596-MMD-NJK (D. Nev.)

Dated: May 12, 2020

/s/ *Jonathan E. Singer*

cc: counsel of record

TABLE OF CONTENTS

Page

TABLE OF CONTENTS (cont'd)

TABLE OF CONTENTS (cont'd)

TABLE OF AUTHORITIES

Page(s)

Cases

TABLE OF AUTHORITIES (cont'd)

TABLE OF AUTHORITIES (cont'd)

STATEMENT OF RELATED CASES

In *Amarin Pharma, Inc. v. Dr. Reddy's Labs., Inc.*, 2:18-cv-01596-MMD-NJK (D. Nev.), which involves the same patents-in-suit, the district court issued a consent judgment based on the judgment in this case on May 4, 2020.

STATEMENT OF JURISDICTION

The district court had subject matter jurisdiction over these patent infringement cases under 28 U.S.C. §§ 1331 and 1338. The district court entered its final judgment on March 30, 2020. (Appx1–71.) Appellants timely filed their notice of appeal on April 2, 2020.

This Court has jurisdiction over the appeal under 28 U.S.C. § 1295(a)(1).

STATEMENT OF THE ISSUES

1. Whether the district court legally erred in its framework for evaluating objective indicia of non-obviousness, by (a) concluding that the claims were obvious before even analyzing the compelling objective indicia evidence, infusing its entire analysis with hindsight; and (b) improperly requiring Amarin to prove every objective indicia or have it count *against* non-obviousness.

2. Whether the district court improperly applied a hindsight-based analysis on motivation to combine and reasonable expectation of success, causing it to ignore significant evidence cutting against Defendants' case and shift the burden to Amarin to prove non-obviousness in an erroneous attempt to fill the evidentiary gaps in Defendants' proof.

INTRODUCTION

The phrase "hindsight is twenty-twenty" is a cliché for a reason. To guard against it, the Supreme Court and this Court require that district courts rigorously apply each of the *Graham* factors, including the common sense objective indicia, ***before*** declaring an invention obvious. Similarly, other concepts like a motivation to combine and reasonable expectation of success exist to avoid a hindsight reconstruction of the claims years after the fact. Because that which might appear obvious in hindsight often was not obvious at all.

In this case, the district court failed to follow these rules and, consequently, fell victim to hindsight. For decades, physicians treated severe hypertriglyceridemia, a genetically-based, life-threatening condition characterized by triglyceride levels of at least 500 milligrams per deciliter (mg/dL), with various medications that all dramatically raised LDL cholesterol ("LDL-C," the so-called "bad" cholesterol), thereby increasing patients' risk of cardiovascular disease. Whatever the treatment, the results were the same—while patients with milder forms of hypertriglyceridemia did not experience substantial LDL-C rises, those with severe hypertriglyceridemia saw dramatic increases in LDL-C.

Amarin's VASCEPA® solved this long-felt need. VASCEPA® is a 4g dose of pure eicosapentaenoic acid ("EPA"), an omega-3 oil. In clinical trials, VASCEPA® lowered triglycerides in patients with severe hypertriglyceridemia, but ***without*** raising

LDL-C. Upon FDA approval in 2012, VASCEPA® thus became the first (and still only) approved severe hypertriglyceridemia medication that does not raise LDL-C.

These issues were largely undisputed at trial. Defendants' expert acknowledged that an ordinary artisan would have understood, at the time of the invention, "that somewhere above 500 milligrams per deciliter the system for clearing triglycerides jams up," thus leading to the problem in the art. And, despite opining Amarin's patents were obvious over the prior art, that same expert conceded: "I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter."

Nonetheless, the district court found the patents-in-suit obvious based on prior art about EPA that had been known for nearly a decade or more, none of which had led skilled artisans to solve the long-felt need met by VASCEPA®. In so doing, the district court put the cart before the horse, finding that "defendants have satisfied their burden" to provide "clear and convincing" evidence of obviousness (prima facie and otherwise) before even considering the proven objective indicia of long-felt need and commercial success. Even then, the district court improperly weighed these two proven objective indicia against those the district court decided Amarin had not proven, as if Amarin's alleged failures to prove praise or skepticism carried independent evidentiary weight. Under this Court's precedent, they do not.

These errors of hindsight were equally as serious in the district court's prima facie case. In analyzing motivation to combine and reasonable expectation of success,

the district court conflated patients without severe hypertriglyceridemia with those with the "jam[med] up" triglyceride clearing system of severe hypertriglyceridemia. Compounding this error, the district court shifted the burden to Amarin to show that these patient groups were different, as opposed to requiring Defendants to prove, by clear and convincing evidence, that they were expected to be the same, inexplicably faulting Amarin for offering "no evidentiary support" for its contentions, despite the mountains of testimony and documents Amarin provided.

Simply put, for seventeen years before the invention, pure EPA had been approved in Japan and was known to lower triglycerides. And, for at least 13 years before the invention, the prior art informed skilled artisans that EPA, like other drugs, did not substantially raise LDL-C in patients ***without*** severe hypertriglyceridemia. Yet no one did what the Amarin inventors conceived—develop a treatment for severe hypertriglyceridemia that, unlike the other prior art treatments, did not raise LDL-C. Only hindsight would suggest that this invention was obvious. The district court's judgment should be reversed.

STATEMENT OF THE CASE

I. The Technology

A. Before the Patented Methods, Treating Patients with Severe Hypertriglyceridemia Resulted in Increased Risk of Cardiovascular Disease

This case generally relates to methods of treating patients who have very high levels of triglycerides in their blood. Triglycerides are lipids, or fats, that naturally exist in the body, and are an important energy source for our bodies. (Appx3; Appx2316–2317 at 1561:21–1562:21 (Toth).) However, when triglyceride levels are too high, serious health effects can follow. (Appx871–872 at 324:5–325:17 (Budoff).) Specifically, triglycerides can build up in the blood and clog arteries, ultimately leading to heart attacks and stroke. (*Id.*)

A person with elevated triglycerides has "hypertriglyceridemia." Not all types of hypertriglyceridemia are created equal, however. At the time of the invention in 2008, skilled artisans recognized three classes of hypertriglyceridemia, based on triglyceride levels in patients' blood: (1) borderline-high (150–199 mg/dL); (2) high (200–499 mg/dL); and (3) very high (≥ 500 mg/dL). (Appx49988–49992; Appx873–875 at 328:17–23 (Budoff); Appx1770 at 1122:5 (Fisher); Appx1438 at 839:9–21 (Heinecke).) These same classifications still exist today. (Appx2322–2333 at 1568:1–1569:24 (Toth); Appx4.)

A patient with "very high" triglycerides (≥ 500 mg/dL) has "severe hypertriglyceridemia"—a condition afflicting roughly 3.5 million Americans. (Appx4;

Appx2466 (Toth).) Unlike the other types of hypertriglyceridemia—which may be caused by an unhealthy lifestyle and poor diet—severe hypertriglyceridemia occurs primarily in patients who, because of their genetics, have extremely elevated levels of triglycerides. (*See e.g.*, Appx47–48 (severe hypertriglyceridemia is "generally a chronic condition caused by genetics"); *see also* Appx879–880 at 332:3–7, 333:17–20 (Budoff) ("Genetic[s] . . . that's the largest and most common cause of very high triglyceride[s]"); Appx1008 at 461:8–11 (Budoff); Appx2325–2326 at 1571:16–1573:25 (Toth); Appx43134; Appx48858.)

Patients with severe hypertriglyceridemia also face a critical, and more urgent, risk than the increased cardiac risk generally associated with high triglycerides: acute pancreatitis, an extremely painful and potentially deadly inflammation of the pancreas. (*See* Appx4; Appx49988–49992; Appx2321–2324 at 1567:2–22, 1569:17–1570:19 (Toth); Appx877–878 at 331:3–20 (Budoff); Appx571 at 72:4–13 (Ketchum).) Consequently, FDA has long recognized severe hypertriglyceridemia as a distinct condition from other forms of hypertriglyceridemia, the only form of the disease to warrant an indication under FDA standards. (Appx2320 at 1566:4–16 (Toth); Appx49988; Appx50675–50676; Appx50357.)

Before Amarin's invention, the approved treatments for reducing triglycerides in severe hypertriglyceridemia patients all resulted in the same, negative consequence:

significant increases in LDL-C.[1] (*See, e.g.*, Appx5 (explaining that "[o]ther treatments for severe hypertriglyceridemia dramatically increase LDL-C levels").) Like triglycerides, cholesterols are naturally existing lipids that can serve important functions. (*See* Appx3; Appx871–872 at 324:16–325:5 (Budoff).) But LDL-C, known as the "bad" cholesterol, "is most associated with heart attacks and strokes." (Appx871–873 at 325:2–326:12 (Budoff).) Thus, as with patients suffering from high triglycerides, patients who have high LDL-C are at increased risk for cardiovascular disease. (*Id.*; Appx4 ("elevated LDL cholesterol is a major cause of CHD"); Appx88292.)

Before the inventions of the patents-in-suit, doctors frequently prescribed LDL-C lowering statins to their patients with severe hypertriglyceridemia to address the LDL-C increases caused by their triglyceride-lowering medications. (Appx2352–2353 (Toth); Appx887–889 (Budoff).) While, at first blush, this might appear to solve the problem, essentially this is robbing Peter to pay Paul. For patients who can tolerate statins, using them to offset LDL-C increases caused by another medication is a poor use of the drug. (Appx2352–2353 (Toth).) Utilizing statins in this way can "burn[] up" the LDL-C-lowering capacity of statins simply to get back to the baseline

[1] LDL stands for "low-density lipoprotein" and is measured by the amount of cholesterol it carries, known as LDL cholesterol, or LDL-C. HDL stands for "high-density lipoprotein, and HDL cholesterol (HDL-C) is commonly known as "good cholesterol."

of where LDL-C was before the severely hypertriglyceridemic patient began taking the triglyceride-lowering drug. (*Id.*)

What was needed, then, was a real solution to this problem—how to treat patients with severe hypertriglyceridemia to reduce the potentially deadly risk of acute pancreatitis, without putting them at an increased risk for cardiovascular disease by increasing their LDL-C. (Appx2466–2470 (Toth); Appx67.) Amarin's inventors solved it.

B. The Prior Art Methods of Treatment for Severe Hypertriglyceridemia

1. Prior Approved Treatments Dramatically Raised LDL-C in Severe Hypertriglyceridemia Patients, But Not in Patients with Less Elevated Triglycerides

At the time of Amarin's invention, there were three FDA-approved drugs, or classes of drugs, for lowering triglycerides in patients with severe hypertriglyceridemia: (1) niacin (vitamin B-3), (2) fibrates, which are derivatives of fibric acid, and (3) Lovaza® (also known as Omacor®), a complex mixture derived from fish oil, which has two primary constituents, EPA and DHA (docosahexaenoic acid). (Appx2328–2330 at 1574:1–1576:15 (Toth); Appx887 at 340:12–17 (Budoff); Appx578 at 79:17–25 (Ketchum); Appx110064; Appx49778–49787; Appx43935–43942; Appx88408–88411; Appx44323–44324.) While these medications all effectively lowered triglycerides in severe hypertriglyceridemia patients, as the experts at trial agreed and the district court found, all also dramatically raised LDL-C in these same patients.

(Appx1450–1451 at 851:15–852:1 (Heinecke); Appx2328–2352 at 1574:1–1575:1, 1598:14–17 (Toth); Appx5.)

Critically, this sharp rise in LDL-C generally was not observed in patients with only borderline high (150-200 mg/dL) or high (200-499 mg/dL) triglycerides. In fact, some of these treatments even ***lowered*** LDL-C levels in such patients, and none raised them substantially.

Niacin is the oldest drug used to treat severe hypertriglyceridemia. (Appx50257.) Since at least 1977, however, it was understood that using niacin to reduce triglycerides in severe hypertriglyceridemia patients led to substantial increases in LDL-C. (Appx110064–110070; Appx2329–2332 at 1575:2-1578:11 (Toth); *see also* Appx2573 at 1789:19–22 (Toth); Appx1450–1451 at 851:15–852:1 (Heinecke) (conceding that niacin raises LDL-C in severely hypertriglyceridemic patients).) One prior art reference described this finding as "of major clinical concern" because the rise in LDL-C was "sometimes quite substantial," and could be "quite atherogenic." (Appx107783.) By contrast, in patients ***without*** severe hypertriglyceridemia, physicians used niacin to ***lower*** both triglycerides and LDL-C. (Appx50257.)

The next class of approved drugs, fibrates, also showed differential LDL-C effects depending on a patient's triglyceride level. (Appx2332–2337 at 1578:12–1583:17 (Toth).) Fenofibrate (marketed as Tricor®) ***reduced*** LDL-C by 13.5% in patients with borderline-high triglycerides. (Appx43934–43950 at 43939–43940;

Appx108954.) And in patients with high triglycerides, fenofibrate did not result in a statistically significant increase in LDL-C. (Appx43939–43940.)

Fibrates acted much differently, however, in severely hypertriglyceridemic patients—those with triglycerides of at least 500 mg/dL. In those patients, fenofibrate increased LDL-C dramatically—by 49.2%. (Appx49340; *see also* Appx2336–2340 at 1582:11–1586:24 (Toth).)

The third FDA-approved drug, Lovaza®, behaved the same. In severe hypertriglyceridemia patients, LDL-C increased 45–50% after Lovaza® treatment, but only 4.5–7% in patients with much lower triglycerides around 275 mg/dL. (Appx48910–48911; Appx2341–2345 at 1587:4–1590:11 (Toth).)

2. The Large LDL-C Increase in Severe Hypertriglyceridemia Patients Was Understood to Result from the Mechanism of Triglyceride Clearance

The understood mechanism behind this phenomenon at the time of Amarin's invention—LDL-C surges for patients with severe hypertriglyceridemia compared to much smaller increases or even decreases for patients with less elevated triglycerides—was explained at trial by Amarin's expert, Dr. Toth. Numerous prior art references corroborated his testimony. (Appx2344–2351 at 1590:12–1597:13 (Toth); Appx44256–44258; Appx48848; Appx48910–48911; Appx43935–43936; Appx43939–43940; Appx107779.)

As noted above, both triglycerides and cholesterol are fats. As a result, neither triglycerides nor cholesterol are soluble in water, so they cannot travel in the aqueous

(or water-soluble) part of the blood. (Appx2316 at 1562:12-17 (Toth).) Rather, proteins called apolipoproteins surround and carry triglycerides and cholesterol for ultimate delivery to cells that need energy. (Appx871–873 at 324:5–9, 325:21–326:12 (Budoff); Appx2316–2317 at 1562:9–21 (Toth).)

Apolipoprotein B ("Apo-B") is the lipoprotein that carries triglycerides and cholesterol, and can be used as an additional predictor of cardiovascular risk. (Appx872 (Budoff); Appx2481 (Toth).) Apo-Bs start out as "very low density lipoproteins" (VLDL), rich in triglycerides, and with a relatively small proportion of cholesterol. (Appx2315–2320 at 1561:21–1563:3 (Toth).) As enzymes remove the triglycerides from the lipoprotein and break them down into fatty acids for use as fuel, the lipoprotein shrinks in size and becomes denser, with relatively more cholesterol and less triglycerides. (*Id.*) In this process, VLDL is first converted to "[i]ntermediate density lipoproteins" (IDL). (*Id.*) As the metabolism continues, these IDL particles are then converted to LDL (*Id.*; Appx872–873 at 325:10–326:12 (Budoff).)

The genetics of severe hypertriglyceridemia patients cause the triglyceride-rich VLDL particles to build up in their blood like a "logjam." (Appx49988; Appx2315–2320 at 1561:16–1566:3; Appx2325–2327 at 1571:16–1573:25 (Toth).) This genetically caused "logjam" manifests itself in dangerously high, sustained triglycerides of at least 500 mg/dL. This logjam was not disputed at trial—Defendants' expert Dr. Heinecke acknowledged that: "we knew [in 2008] that somewhere above 500

milligrams per deciliter the system for clearing triglycerides jams up." (Appx1395–1396 at 796:21–797:2 (Heinecke).)

While scientists continue to study their precise mechanisms of action even today, at the time of Amarin's invention, existing triglyceride-lowering treatments were all believed to break this logjam by activating the enzymes to convert the large volume of excess VLDL particles to LDL particles. As a consequence, large surges in LDL resulted, dramatically increasing LDL-C. (Appx2344–2351 at 1590:12–1597:13; Appx2315–2318 at 1561:16–1564:22 (Toth) ("But if you break that logjam and suddenly you activate the enzyme somehow, then you can see a large surge in the production of that LDL and the LDL[-C] levels would rise.").)

The prior art consistently reflected this understanding, whether it occurred with Lovaza®, fibrates, niacin, or even diet. For example, a 2008 article by Bays, et al. about Lovaza® stated:

> ***As with fibrates***, the degree of LDL-C elevations observed with [omega-3] treatment is ***generally related to the pretreatment TG levels***. [Omega-3 fatty acids] increase[] LDL-C levels the most in patients with the highest pretreatment TG levels. ***The reason for the increased LDL-C levels with [omega-3 fatty acids] is related to the increased conversion of VLDL particles to LDL particles***.

(Appx44247–44265 at Appx44256–44258[2]; Appx2350–2351 at 1596:11–1597:13 (Toth); *see also* Appx107779 (noting phenomenon even when triglycerides are lowered through diet in patients with severe hypertriglyceridemia).)

[2] All emphasis added unless noted otherwise.

Similarly, a 2007 clinical review by McKenney commented:

> ***As with fibric acid derivatives (fibrates) and nicotinic acid (niacin***), reductions in triglycerides and very-low-density-lipoprotein (VLDL) cholesterol [achieved by DHA and EPA] are generally greater in patients with higher baseline triglyceride levels. ***An increase in low-density-lipoprotein (LDL)*** and high-density-lipoprotein (HDL) cholesterol can accompany a reduction in triglycerides; ***the higher the baseline triglyceride level, the greater these lipids may be increased***.

(Appx48844–48856 at Appx48848; *see also* Appx2345–2349 at 1591:12–1595:3 (Toth).) McKenney further observed that, under the influence of omega-3 fatty acids, "the conversion of VLDL to LDL particles increased 93%," explaining the rise in LDL-C in severe hypertriglyceridemia patients: "[t]he results also show that VLDL particles ***are rapidly converted to LDL particles, thus explaining why LDL cholesterol levels may rise in patients with very high triglycerides when given [omega-3 fatty acid] therapy***." (Appx48848.)

Skilled artisans thus did not consider the surge in LDL-C as a mere "side effect" of certain medications. Rather, they understood it as a function of the mechanism of clearing the triglycerides themselves, which, in patients with severe hypertriglyceridemia, malfunctions because of their genetics. (*See, e.g.*, Appx2344–2352 (Toth).)

Because of this surge, physicians generally had to prescribe a statin in an effort to negate the rise in LDL-C. In addition to the issue of "burning up" the statins' LDL-C lowering capacity, clinicians also recognized that patients are far less likely to take consistently two pills rather than just one—indeed, most patients stop taking

statins after six months. (Appx2352–2353 (Toth); Appx1412–13 at 813:8–814:2 (Heinecke).) Moreover, when a particular patient could not tolerate statins, there were limited options for addressing the dramatic rise in LDL-C. (Appx2352–2353 (Toth).)

Before 2008, there was thus a pressing need for a safe, well-tolerated treatment that could successfully reduce triglycerides in severe hypertriglyceridemia patients, thereby addressing the risk of pancreatitis, but ***without*** causing a surge in LDL-C and the corresponding increase in cardiovascular risk. (Appx2466–2470 (Toth); Appx67.)

3. The State of the Prior Art Relating to EPA

Before Amarin's inventors conceived their invention, others had used EPA to treat lipid disorders, but not for treating the severe hypertriglyceridemic population. For example, a pure EPA product known as Epadel® had been on the market in Japan since 1991. (Appx677; Appx88321–88334.) But Epadel® was not approved to treat severe hypertriglyceridemia. (Appx2427–2430 (Toth); Appx4151–4152 (Manku).)

Given EPA's prior long-standing use in Japan, there were many published clinical studies relating to treating hypertriglyceridemia with pure EPA before Amarin's invention. All involved patient groups that, on average, had either normal, borderline high, or high levels of triglycerides, but not severe hyperglyceridemia. Among these was the study relied on heavily by the district court in invalidating Amarin's patents, the Mori reference ("Mori") (Appx88480–88489).

Mori discloses a clinical experiment from 2000 that studied the separate effects of 4g of pure-EPA, 4g of pure-DHA product and an olive oil placebo in 56 patients with "***mild*** hyperlipidemia." (Appx88480.) As the experts at trial agreed, mildly hyperlipidemic patients have only modestly elevated triglycerides, i.e., under 200 mg/dL. (Appx1429–1430 (Heinecke); Appx1494–1495 (Heinecke); Appx2394–2395 (Toth).)

Mori reports that both DHA and EPA showed about the same triglyceride-lowering ability, roughly 20%. (Appx88483; Appx2398–2399 (Toth).) As to LDL-C, Mori reports DHA showed a small, but statistically significant rise (8%), while EPA showed a non-statistically significant increase (3.5%). (Appx88483; Appx2396–2397 (Toth).) Mori also reports DHA and EPA's effects on HDL, blood glucose, and LDL particle size, concluding that that "EPA and DHA had differential effects on lipids, fatty acids, and glucose metabolism in overweight men with mild hyperlipideimia."[3] (Appx88480.) As between the two, Mori expresses a preference for DHA: "[d]espite an increase in LDL cholesterol after DHA supplementation, the increased LDL particle size may represent a shift to less atherogenic particles, in which case the parallel increase in HDL cholesterol and decrease in triacylglycerol may represent a

[3] Regrettably, the district court presented Mori's conclusion without reference to Mori's mildly hyperlipidemic population as follows: "Mori concludes that 'EPA and DHA had differential effects on lipids.'" (Appx25.)

more favorable lipid profile than that seen after EPA supplementation." (Appx88487; *see also* Appx2403–2405 (Toth).)

While, at Defendants' urging, the district court seized on the LDL-C difference between DHA and EPA in Mori in assessing obviousness, Mori itself found it unremarkable. In fact, Mori comments about the ***rise*** in LDL-C observed in ***both*** groups and hypothesizes that it results, in part, from the same mechanism described in the literature discussed above—an increased conversion of VLDL to LDL:

> Although the LDL-Cholesterol concentration increased after EPA and DHA intakes, the increase was significant only after DHA. The increased LDL-cholesterol concentration may relate to the hypotriglyceridemic effects of these fatty acids. n-3 Fats reduce hepatic VLDL synthesis, VLDL secretion, or both with the result that the smaller VLDL particles formed are more readily converted to LDL than the larger VLDL particles.

(Appx88485.)

In this regard, Mori is typical of the prior art on EPA before Amarin's invention—studies showing a variety of effects of EPA on patient groups with moderately elevated, but not severely elevated, triglycerides. As Defendants' expert Dr. Heinecke conceded: ". . . I don't think there's any evidence in the prior literature about what the impact of EPA would be on LDL cholesterol in patients above 500mg per deciliter." (Appx1398–1399.)

Of a piece with Mori were two other Japanese references featured in the district court's opinion: Hayashi and Kurabayashi. (Appx88363–88372; Appx88400–88407.) Hayashi is a 1995 study of 28 patients with mean triglyceride levels of 300 mg/dL. In

the paper, 1.8 g of EPA lowered triglycerides, but without an increase in LDL-C. (Appx88366–88367; Appx2411–2412 (Toth).) And, while the district court found that Hayashi included at least one patient with triglycerides above 500 mg/dL, the experts agreed that Hayashi reported no LDL-C data for any patients with triglycerides above 400 mg/dL. (Appx1493–1494 (Heinecke); Appx2408–2413 (Toth).) Nor could it have, because, as the experts also agreed, Hayashi calculated LDL-C by the Friedewald equation, which is inaccurate above 400 mg/dL triglycerides. (Appx1398–1399 (Heinecke); Appx1493–1494 (Heinecke); Appx2412–2413 (Toth).)

Kurabayashi is even further afield. Kurabayashi is a year 2000 study comparing the effects of estrogen and estrogen plus 2g of EPA in 141 menopausal women. (Appx88400.) Both groups had ***normal*** average triglycerides, around 135 mg/dL. (Appx88403; Appx 1429 (Heinecke); Appx1495–1496 (Heinecke); Appx2415–2416 (Toth); Appx2432 (Toth).) Table 2 of Kurabayashi reports that triglycerides declined significantly in the EPA plus estrogen group, and went up non-significantly in the estrogen-only group, while LDL-C went down significantly in both groups. (Appx88403.) In addition, Table 3 shows that Apo-B went down significantly in the EPA plus estrogen group, but this finding was not significantly different from the

estrogen only group, where Apo-B declined only numerically.[4] (Appx88404.) Notably, Kurabayashi excludes any patients with triglycerides above 400 mg/dL. (Appx88401.)

Accordingly, at the time of the invention, no one had even thought to try the widely-studied EPA in a severely hypertriglyceridemic population before the Amarin inventors conceived that it would solve the problem that the art faced—namely, how to avoid the LDL-C surge caused by lowering triglycerides in patients with severe hypertriglyceridemia.

II. Amarin's Patented Method of Treatment

A. The Inventors Saw New Potential in an Old Product, and Conceived of Pure EPA as an Effective Treatment for Severe Hypertriglyceridemia That Avoided Increasing LDL-C

Against this background, Amarin developed its groundbreaking and successful treatment for severe hypertriglyceridemia. Rather than developing a new active ingredient, the inventors instead looked to the old ingredient that had been on the market in Japan for over 15 years—EPA. Their insight—contrary to the common wisdom of the time—was that pure EPA could effectively lower triglycerides in patients with severe hypertriglyceridemia ***without*** causing the typical surge in LDL-C.

[4] Unfortunately, in reprinting Table 3 of Kurabayashi's Apo-B results, the district court's opinion cut off the inter-group statistical comparison. (*Compare* Appx30 *with* Appx88404.) Defendants' proposed findings of fact did so as well. (Appx102826.)

This insight led to the patents-in-suit, embodied in Amarin's novel and life-saving drug, VASCEPA®.

Dr. Mehar Manku was the lead inventor on the project. He joined Amarin as Vice President of Research and Development in November 2004.[5] At the time, Amarin had roughly a dozen employees. (Appx775 (Ketchum).)

Before joining Amarin, Dr. Manku worked at Amarin's predecessor Laxdale, and, before that, had "work[ed] in the area of fatty acids as medicines for . . . almost 40 years or so and worked extensively using EPA." (Appx4142; Appx4121 (Manku).) At Laxdale, he studied the use of purified EPA for neuropsychiatric indications such as depression, schizophrenia, and Huntington's Disease. (Appx4128-4130, Appx4135-4137.) He brought this work with him to Amarin. And while the clinical trials on the neuropsychiatric conditions did not meet their endpoints, these trials nonetheless generated significant, non-public data. (Appx4136–4137, Appx4144–4146; Appx90356–90358; Appx43697–43699.)

These data keyed Dr. Manku into EPA's potential as a possible therapy for severe hypertriglyceridemia, knowing that the then-available treatments for that condition caused a significant rise in LDL-C and there was a need for a treatment option that did not. (Appx4190–4194; Appx4149–4151 (Manku); *see also* Appx2469–2471 (Toth).) This is because schizophrenia drugs usually drive large increases in

[5] Dr. Manku is a resident of Birmingham, England, and had retired from Amarin at the time of trial. (Appx4119; Appx4163.) He testified by deposition.

triglycerides, but the blood data from the neuropsychiatric clinical trials showed that administering EPA to these patients not only reduced triglycerides, but did so without raising LDL-C. (Appx4273–4275; Appx4206.) Digging deeper into these results, Dr. Manku gained significant insight about lipid blood levels and, importantly, about how EPA works in the body. (Appx4195–4204.) From these data, combined with his own knowledge, by 2007, Dr. Manku concluded that DHA—the other primary constituent of Lovaza®—"actually interferes with the mode of action of EPA." (Appx4197; Appx4162–4163.)

From this conclusion, Dr. Manku conceived that purified EPA by itself, without interference from DHA, could reduce triglycerides in severe hypertriglyceridemia without raising LDL-C. (Appx4120; Appx4243; Appx4159–4163.) He thus decided to study pure EPA for this purpose, even though, prior to that, no one had thought to look at "what would be the clinical benefit" of using pure EPA in patients "with very high triglycerides of over 500." (Appx4198–4199.)

Dr. Manku's colleagues at Amarin did not share his optimism. (Appx4251–4252.) As he testified, "all the experts that we were talking to" at the time of the invention were saying, "[l]ook there is LDL increase in over 500 patient population. It's a phenomena, you cannot stop it, it will happen because that is the physiological mechanism . . ." (Appx4252; Appx4221–4224 (explaining that "[t]he experts were not in favor of" his idea of using EPA in patients with very high triglycerides.) Dr. Manku sent his colleagues publications to try to convince them that "mechanism wise

this is going to be a different type of mechanism." (Appx4252.) But nonetheless, Dr. Manku had "great difficulty in convincing individuals within the company, and outside the company, on why ethyl-EPA would be effective in lowering triglycerides significantly in [the] very high patient population, with those over 500 [mg/dL], and would not affect other lipid parameters." (Appx4193.) Indeed, it took him a "long time" to convince them. (Appx4194.)

Dr. Manku used the insights gleaned from the neuropsychiatric clinical data, along with "bits and pieces of information, although not in the right population" from the prior art to help convince his colleagues that he was right. (Appx4273–4274; *see also* Appx44204–44205 (discussing EPA's effects in schizophrenia patients); Appx44069–44072 (explaining views on how EPA affects lipids and biomarkers); Appx44196–44203.) As the company's expert on omega-3 oils, Dr. Manku sent his colleagues examples of this information to "educate them about the literature that's available related to EPA." (Appx4245–4246.) He listened in on calls with potential investors and sent e-mails to colleagues to convince them that his insight was correct and that expensive clinical trials in patients with severe hypertriglyceridemia would not be a waste. (Appx4254; Appx4260–61.)

Those "bits and pieces of information" in the art showed that omega-3 fatty acids like EPA had some potential beneficial outcomes, as in Mori, Hayashi and Kurabayashi, but "[t]he direction and magnitude of change does vary from study to study depending on size, ***nature of population***, and duration of treatment, and dose

of [purified fatty acids]." (Appx90286–90288.) After convincing his colleagues, Dr. Manku worked with them, using the information that he provided, to develop the scientific rationale for the development project, ultimately meeting with FDA to help construct the clinical trials. (Appx4229–4230.)

B. Amarin's Clinical Trials on EPA Surprisingly Showed a Reduction in Triglycerides without a Corresponding Increase in LDL-C in Severe Hypertriglyceridemia Patients

Amarin moved forward with a clinical program to test pure EPA in severe hypertriglyceridemia patients beginning in late 2008. (Appx4193–4194 (Manku); Appx571–573 (Ketchum).) Before actually starting the trials, Amarin hosted a group of experts to get their views on the clinical trial design and the effects that EPA might have. (Appx43971; Appx43974–43977; *see also* Appx4985–4986.) In advance of the meeting, Amarin provided extensive materials to the experts, including a summary of information about prior art studies of EPA's effects on LDL-C, including Mori. (*E.g.*, Appx43970; Appx43986; Appx43992; Appx4276–4277.) Nonetheless, as reflected in contemporaneous notes from that meeting, these experts remained skeptical that EPA would reduce triglycerides in severely hypertriglyceridemic patients without substantially raising LDL-C: "LDL-C is likely to go up as it does with virtually all tg lowering therapies in this group of patients." (Appx47719–47722 at Appx47720; Appx4985–4992 (Osterloh).)

These experts turned out to be wrong. Amarin's MARINE clinical trial, which examined the effects of Amarin's purified EPA formulation on severe

hypertriglyceridemia patients, showed that 4g of EPA effectively reduced triglycerides by 33%, but without the typical surge in LDL-C. (Appx47963–Appx47964; Appx47929–47949; Appx594–596 (Ketchum); Appx2358–2360 (Toth).) In addition, 4g of EPA (though not 2g) surprisingly led to a 9% reduction in Apo-B. (Appx47937–47938.) The MARINE Clinical Study Report notes the difference between its results and the prior art treatments for this patient population: "[i]n contrast to other TG-lowering agents, the reduction in TG levels was not associated with an elevation in LDL-C levels compared to placebo." (Appx47870; *see also* Appx2358–2359 (Toth).)

Based on the MARINE study, FDA approved VASCEPA® on July 26, 2012 "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia." (Appx43106; *see also* Appx50675–50688; Appx550–551 (Ketchum); Appx564 (Ketchum).) Upon approval, FDA publicly released a 2011 Medical Review, which detailed FDA's evaluation of Amarin's clinical data and the rationale for recommending FDA approval. (Appx601–602 (Ketchum); Appx43682–43689.)

The Medical Review identified the "Important Safety Issues" that FDA recognized in prior treatments, highlighting that "the only other FDA approved omega-3 fatty acid product (Lovaza)" has "four areas of potential safety concern," beginning with "increases in LDL-C." (Appx43686.) Consistent with the understanding in the art of the mechanism of reducing triglycerides in patients with

severe hypertriglyceridemia, FDA explained that "[t]he increase in LDL-C" observed with Lovaza® "is thought to be due to the . . . enhance[d] . . . conversion of [VLDL] and [IDL] to LDL-C." (Appx43686; *see also* Appx1460–1463 (Heinecke) (admitting that FDA "continued to believe" this was the mechanism for Lovaza® even in 2011).) The Review goes on to conclude: "Vascepa 4 g did not increase LDL-C levels," thus eliminating the "Important Safety Issue" of increased LDL-C. (Appx43729–43730.)

Even before its approval, when only preliminary, non-peer-reviewed results were available, clinicians recognized VASCEPA®'s ability to lower triglycerides in patients with severe hypertriglyceridemia while avoiding the surge in LDL-C that had plagued the prior art. (*See* Appx2360–2369 (Toth); Appx2476–2477 (Toth).) For example, a prominent cardiologist from the Cleveland Clinic described the early results as a "real advance in the treatment of elevated triglycerides" because "[i]t gives you all the benefit without the downside." (Appx86649–86651 at Appx86650; Appx2364–2366 (Toth); Appx2477 (Toth).) This same cardiologist hailed the results as showing that "[t]here's still room for small companies to do innovative things in this field." (Appx86650; *see also* Appx48698–48706 at Appx48702.)

Consistent with this early recognition, VASCEPA® has seen great success in the marketplace, with an average annual growth rate of 54% since launch and net sales of $226 million in 2018. (Appx39–42; Appx2124; Appx2127–2129 (Nicholson).) But Amarin did not sit back and simply reap the profits. Instead, Amarin poured much of the revenues from VASCEPA® sales into further clinical research. In a study of over

8000 patients over five years called REDUCE-IT, Amarin evaluated the effectiveness of VASCEPA® as an add-on to statin therapy in reducing major cardiovascular events in patients with more moderately elevated triglycerides. (Appx50691–50709; *see also* Appx639–640 (Ketchum).)

The results of REDUCE-IT, first announced in 2018, were an additional great advance for cardiovascular health. Compared to statins alone, VASCEPA® showed a 25% reduction in major cardiovascular events. (Appx50819–50825; Appx2370–2373 (Toth).) Based on those results, in December 2019, FDA approved VASCEPA® for a second indication as an add-on to statin therapy to reduce the risks of heart attacks, strokes and other cardiovascular events in certain patient populations. (Appx50675; Appx38.)

In a press release about this additional approval, FDA recognized that "VASCEPA is the first FDA-approved drug to reduce cardiovascular risk among patients with elevated triglyceride levels as an add-on to maximally tolerated statin therapy." (Appx50672–50673; *see also* Appx2379 (Toth); Appx1450–1451 (Heinecke).) The results of REDUCE-IT have understandably been met with widespread enthusiasm in the field. (Appx2377–2387 at 1625:22–1633:5 (Toth); Appx49765–49766; Appx48717–49719; Appx47464–47492; Appx49004–49006; Appx48737–48737; Appx660 (Ketchum).)

C. Amarin's Patents-in-Suit Claim Its Invention of Treating Severe Hypertriglyceridemia without Raising LDL-C

Amarin's six patents-in-suit cover its innovative methods of treatment of using pure EPA to treat severe hypertriglyceridemia. (Appx72–207.) The ten claims asserted at trial generally cover methods of reducing triglycerides in patients with severe hypertriglyceridemia without raising LDL-C levels by administering pure EPA. Claim 1 of the '728 patent is representative:

> 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.

(Appx92.)

During prosecution of its patents, Amarin cited each of Mori, Hayashi, and Kurabayashi. (Appx73–80.) In allowing Amarin's first patent, the '728 patent-in-suit, the Examiner focused on the most important aspect of Amarin's invention—that by using 4g of pure EPA to treat severe hypertriglyceridemia, the inventors filled the long-felt need for a severe hypertriglyceridemia treatment that did not result in elevated LDL-C. (Appx57815–57821 at 57820.) The Examiner also commented

favorably on the surprising reduction in Apo-B that Amarin's invention achieved, as demonstrated in the MARINE clinical trial. (Appx57818–57819.)

III. The Present Litigation

VASCEPA®'s success attracted potential generic competition. On the four-year anniversary of FDA approval, each of the two generic Defendants in this case—Hikma and Dr. Reddy's—filed abbreviated new drug applications seeking FDA approval to market generic versions of VASCEPA®. (*See* Appx5; Appx7–10.)

After receiving paragraph IV letters from each of the Defendants, Amarin filed suit against both for patent infringement in the District of Nevada. (Appx1–2.) Defendants answered, asserting non-infringement and invalidity. (Appx2.) On summary judgment, the district court ruled that defendants had waived any challenge to the patents-in-suit under 35 U.S.C. § 112. (Appx103437–103440.) The district court then held a seven-day bench trial in January 2020 to resolve infringement and obviousness. (*See* Appx1.)

On infringement, Defendants' primary argument was that their labels would not induce infringement because, according to them, the labels did not instruct doctors to administer EPA for at least 12 weeks, as required by all the claims. (*See generally* Appx102740–Appx102744.) The district court correctly rejected this argument, explaining that the evidence at trial "established that severe hypertriglyceridemia generally has a genetic component, meaning that it is usually a chronic condition requiring long-term treatment." (Appx47–48.) Thus, as the district

court found, if approved, Defendants' labels would induce infringement of this limitation, as well as the other limitations Defendants challenged, which, in the main, related to not raising LDL-C and lowering Apo-B. (Appx47–54.)

Where the district court went wrong, though, was in its analysis and conclusions with respect to obviousness. At trial, Defendants asserted that the challenged claims would have been obvious over four "key" references: (1) a physician's desk reference ("PDR") for Lovaza® ("Lovaza® PDR"); (2) Mori; (3) Hayashi; and (4) Kurabayashi. (Appx1317–1318 (Heinecke); Appx102745–102750; Appx102820–102826; Appx103349–13351.) According to Defendants, a skilled artisan would have modified the Lovaza® PDR method—treating severe hyperglyceridemia with a mixture of components that included EPA and DHA—to using only EPA because Mori, Hayashi and/or Kurabayashi made it obvious that EPA would not increase LDL-C in patients with severe hypertriglyceridemia, unlike Lovaza®. (*See, e.g.* Appx103349–103351; Appx56–61.)

Defendants' theory was, and is, pure hindsight. While it may seem obvious in 2020 that using EPA alone would treat severe hyperglyceridemia without raising LDL-C after Amarin had already figured it out, no one else had figured this out during the nearly two decades leading up to the time of the invention, when an approved EPA product was on the Japanese market. (*See, e.g.*, (Appx677; Appx88326–88334; Appx4151–4152 (Manku); Appx1488–1489 (Heinecke).) Even the question Defendants framed for the district court to consider—that a skilled artisan would

investigate Lovaza® to determine whether DHA or EPA or both caused LDL-C to increase—was based on hindsight. (*See e.g.*, Appx103349–103350; Appx57.) Only someone who knew the answer would ask the question this way, instead of believing that the disease itself was responsible for the increase.

The district court fell victim to this hindsight. Unfortunately, the court adopted a framework for analyzing obviousness that this Court has cautioned against and that can lead to hindsight—first considering a "prima facie" case of obviousness before weighing objective indicia such as the long-felt but unmet need for a product like VASCEPA®. Specifically, in its legal analysis, the district court found that "[a]s an initial matter, the Court is persuaded that Defendants presented clear and convincing evidence at Trial that all Asserted Claims are invalid as obvious." (Appx57; *see also* Appx59 ("The Court therefore finds that Defendants established by clear and convincing evidence at Trial that all Asserted Claims are *prima facie* obvious.").) Only after this did the district court consider the objective indicia, requiring them to "overcome" the prima facie case of obviousness. (*See* Appx69.)

With regard to the purported prima facie case, in finding that a skilled artisan would have been motivated to modify the treatment of the Lovaza® PDR in line with Defendants' theory, the district court conflated the severely hypertriglyceridemic patient population in the Lovaza® PDR with the more mildly afflicted populations in Mori, Hayashi, and Kurabayashi. (Appx57–61.) In so doing, the district court: 1) ignored the extensive testimony and publications about why drugs might cause a

dramatic rise in LDL-C in severe hypertriglyceridemia, while not causing it in milder conditions; 2) failed even to mention the differing effects of Lovaza® and fibrates in the two populations; and 3) dispensed with evidence on niacin's differential effects as being "from 1977" despite general agreement on these effects. (Appx60.)

The district court's analysis of reasonable expectation of success was no better. Based on nothing more than the conceded fact that a skilled artisan would expect triglyceride-lowering drugs to lower triglycerides in patients above 500 mg/dL, as they had below 500 mg/dL, the district court asserted that Amarin's contentions about the differential LDL-C rise "lack[ed] evidentiary support," despite the evidence discussed above. (Appx60.) In a passage of the opinion strikingly copied verbatim from Defendants' proposed findings (*compare* Appx60–61 *with* Appx102950), the district court even faulted Dr. Toth for "cit[ing] 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." (Appx60.) Putting aside that Dr. Toth presented lengthy testimony on this issue, backed up by the prior art (Appx2328–2352 (Toth); Appx110064–110070; Appx43934–43950; Appx48910–48911; Appx44247–44265; Appx48844–48856), it was not Amarin's burden to prove this difference—rather, it was Defendants' burden to prove that skilled artisans would reasonably expect a lack of one. They utterly failed to do so.

Equally flawed was the district court's consideration of the objective indicia. For one, despite crediting Amarin's evidence of a long-felt but unmet need and

commercial success, the district court found that "these secondary considerations [were] outweighed by the fact that the Court found Plaintiffs' other proffered secondary considerations favor Defendants"—in essence finding that Amarin would have been better off had it not presented evidence concerning these other objective indicia. (*See* Appx69.) As to those other indicia, the district court: 1) wrote off powerful evidence of skepticism based on an apparent and erroneous belief that those expressing skepticism were not aware of Mori (Appx67–68); 2) wrongly rejected evidence of praise from independent physicians as too "qualified and equivocal" merely because the doctors were cautious about interpreting early results that had not yet been peer reviewed (Appx68–69); and 3) erroneously discounted Amarin's evidence of unexpected benefits because the court wrongly thought that Kurabayashi had not been cited to the patent office (Appx66).

To remedy these errors in the district court's obviousness analysis, Amarin now appeals.

SUMMARY OF THE ARGUMENT

The district court's obviousness judgment suffers from fundamental errors. First, the district court erroneously bifurcated a "prima facie" case of obviousness and the objective indicia of non-obviousness. By so doing, the district court fell into the trap of hindsight—dismissing powerful objective evidence of non-obviousness because the court had already decided the claims were obvious. Compounding this error, the district court inexplicably "weighed" the objective indicia that the court ruled Amarin had proven against those that it ruled Amarin had not. When the objective indicia receive proper weight, Amarin's claims are plainly non-obvious.

Hindsight also infected the district court's analysis of the prima facie case. Before Amarin's invention, all prior treatments for severe hypertriglyceridemia had the same effect—a dramatic rise in LDL-C—not seen in patients with milder forms of the disease. The district court disregarded this key difference, never even explaining the underlying science of the disease. In the process, the court improperly shifted the burden to Amarin, requiring it to prove that triglyceride-lowering drugs produced different effects depending on patients' baseline triglyceride levels. And while Amarin did just that, the end result of the district court's analysis was an obviousness judgment that effectively ruled that ordinary artisans had a reasonable expectation of producing that which had never been achieved before Amarin's inventions—a triglyceride-lowering therapy for severe hypertriglyceridemia that did not dramatically raise LDL-C. The district court should be reversed.

STANDARD OF REVIEW

"Obviousness is a question of law based on underlying factual findings." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012). When reviewing a district court's obviousness judgment after a bench trial, this Court "review[s] its legal conclusions de novo, but [] review[s] its underlying factual findings for clear error." *Id.* at 1069.

ARGUMENT

I. The District Court's Obviousness Judgment Should Be Reversed.

A. Hindsight Bias Infected the District Court's Analysis of Objective Indicia

As this Court has repeatedly recognized, careful consideration of objective indicia of non-obviousness serves as an important "guard against slipping into the use of hindsight" and disciplines courts to "to resist the temptation to read into the prior art the teachings of the invention in issue." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc) (internal quotation marks omitted). Indeed, objective indicia "may often be the most probative and cogent evidence in the record." *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008). This is because the objective indicia often provide an "unbiased indication" as to "how the patented device is viewed in the marketplace, by those directly interested in the product"—rather than trying to piece together whether an invention is obvious after all of the work of invention has been done based on a "battle of scientific experts." *See Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1370 (Fed. Cir. 2012).

Accordingly, the objective evidence can carry the day, even where (with the aid of hindsight) an invention may seem obvious. For example, in *United States v. Adams*, the Supreme Court determined that Mr. Adams' claimed water battery was non-obvious "[d]espite the fact that each of the elements of the [claimed invention] was

well known in the prior art." 383 U.S. 39, 51 (1966). Primary among the reasons for reaching this result, the Court noted that "the Adams battery 'wholly unexpectedly' has shown 'certain valuable operating advantages over other batteries' while those from which it is claimed to have been copied were long ago discarded" and that noted experts at the time initially doubted the invention then celebrated it. *See id.* at 51–52. Similarly, this Court has found that objective indicia are particularly important where, "once the problem and solution appear together in the patent disclosure, the advance seems self-evident." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1379 (Fed. Cir. 2012). Thus, even where "the claims contained elements that were not new," the claim could still be non-obvious based on the objective indicia. *Kinetic Concepts*, 688 F.3d at 1369–70.

Here, the district court made two structural errors regarding objective indicia evidence. First, the district court relegated them to secondary status, by reaching a conclusion that the claims were obvious before even considering the objective indicia. In this process, the district court also clearly erred in finding a lack of skepticism and praise.[6] Second, the district court discounted evidence of long-felt need and commercial success because the district court found that other objective indicia were

[6] The district court also erroneously rejected unexpected results, but based that finding primarily on its prima facie case. (Appx66.) Accordingly, we address that error primarily in Section B, below.

not proven. Before discussing these errors, though, we first explain why the objective indicia are a powerful and unbiased indication that Amarin's claims are non-obvious.

1. Objective Indicia Are Powerful Evidence in this Case and Confirm the Claims Are Not Obvious

This case is a textbook example of why objective indicia serve as an important, unbiased check against hindsight. As noted above, the district court found Amarin's claims obvious over the Lovaza® PDR in light of Mori, and, secondarily, Hayashi and Kurabayashi. (Appx57–61.) According to the district court, the Lovaza® PDR taught treating patients with severe hyperglyceridemia with a "commercially-available preparation of EPA and DHA administered at 4 grams/day," but which caused a "significant increase" in patients' LDL-C. (Appx23–24.) Also according to the district court, Mori taught that EPA effectively lowers a patient's triglycerides without raising the patient's LDL-C (albeit in a completely different population of patients, but let's just brush over that). (Appx24–25.) Obviously, a person trying to solve the problem of Lovaza® (a rise in LDL-C levels) would simply just take out the DHA (and the other constituents in Lovaza®) and use pure EPA.

This theory, though, falls completely apart when the objective indicia are considered. For example—if (as the district court found) it was so obvious that pure EPA would be an effective treatment for severe hyperglyceridemia without raising LDL-C, why did no one else undertake this solution before Amarin? The problem of LDL-C increases in treating severe hypertriglyceridemia had been recognized since the

1970s, and pure EPA products had been on the market in Japan for over fifteen years. (Appx88327; Appx4151–4152 at 40:24-41:15 (Manku); Appx1488–1489 (Heinecke).) Mori itself dates from 2000—almost a decade before Dr. Manku conceived his invention. (Appx88480.) And Mori's purported key finding—that EPA is effective to treat patients with less severe forms of hypertriglyceridemia without raising LDL-C levels—is no different than those in other studies from even earlier, including Hayashi from 1995. Yet, despite all of this information being available, no one before Dr. Manku thought to use this supposedly obvious way to treat severely hypertriglyceridemic patients. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013) (rejecting obviousness finding where "Turi was publicly available in the prior art for twenty-two years before the '013 patent was filed, yet there is no evidence that anyone sought to improve Turi with vitamin D").

Indeed, the obviousness story here appears to go backwards. Mori not only significantly pre-dates Dr. Manku's invention, it also significantly pre-dates Lovaza®, first approved in the United States in 2004. (*Compare* Appx88408–88409 *with* Appx88480.) Normally, one would think that if Mori so clearly taught that using EPA was an effective treatment for severe hypertriglyceridemia that, unlike all previous treatments, didn't raise LDL-C, the makers of Lovaza® or some other drug developer would surely have turned to at least study pure EPA as a treatment for severe hypertriglyceridemia. After all, based on the opinion's reasoning, the prior art already had made it "obvious" for years that pure EPA would not raise LDL-C in severe

hypertriglyceridemia patients, while DHA would. But nobody did. They instead chose to use a mixture of predominantly EPA and DHA, which resulted in the typical rise in LDL-C. (Appx44323–44324.) Defendants' theory, adopted by the district court, makes no logical sense.

All of this is evidence of a long-felt, but unmet need. Dating back to the 1970s, there was a need for a treatment that could reduce severe hypertriglyceridemic patients' triglycerides without concomitantly raising their cardiovascular risk by substantially increasing LDL-C. (Appx2329–2332 at 1575:2-1578:11; Appx2466–2471 at 1712:6–1717:2 (Toth).) The previous answer to this problem—prescribing a statin—was inadequate, as any additional drug raises the possibility of new side effects, because patients are far less likely to take two pills rather than just one, and because most patients simply stopped taking statins. (Appx1412–13 at 813:8–814:2 (Heinecke).) And, for some patients—specifically patients who can't tolerate statins—this "solution" was no solution at all. (Appx2352–2353 (Toth).)

And while the district court understood that Dr. Manku's invention solved this long-felt need, it failed to give proper weight to this finding because it had already found the invention obvious. As this court has explained, "[e]vidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple*, 839 F.3d at 1056. Yet instead of asking how its finding that the inventors solved a long-felt need affected the overall obviousness analysis, the

district court dismissed it almost out of hand, remarkably stating that though the "Asserted Claims represent an improvement"—that improvement was "a *prima facie* obvious one." (Appx67.) This stands the objective consideration of long-felt need on its head, by giving it ***less*** weight because a district court has already found an invention *prima facie* obvious.

The district court also failed to ask or answer ***why*** this long-felt need persisted for so long. The answer, as Amarin demonstrated at trial, is that skilled artisans would have believed that pure EPA would have the same effect on patients with severe hypertriglyceridemia that the other approved treatments before VASCEPA® had—a "surge" in LDL-C. (*See supra* Fact Section I.B.3.) As he testified, Dr. Manku had "great difficulty in convincing" his colleagues at Amarin and those outside the company as to "why ethyl-EPA would be effective in lower[ing] triglycerides significantly in very high patient population, with those over 500 [mg/dL], and would not affect other lipid parameters." (Appx4193 at 82:9–18.)

Again, while the district court recognized that Dr. Manku faced skepticism in fact, because it had already concluded the invention was obvious, it was unwilling to give this powerful evidence any real weight. The Court cited internal meeting notes from a panel of experts hired by Amarin who predicted before the MARINE trial that "LDL-C is likely to go up as it does with virtually all tg lowering therapies in this group of patients." (Appx68; *see also* Appx47720.) Yet, because the district court had already formed an opinion on obviousness, it worked hard to minimize the

importance of this evidence, rejecting it because the experts' view "does not appear to account for Mori." (Appx68.) In other words, the experts' skepticism was not entitled to weight because the district court had already decided it was wrong—i.e., that Mori taught that LDL-C would not go up in patients with severe hypertriglyceridemia, even though Mori relates to a different patient population, those with only mildly elevated triglycerides. The district court never considered whether the experts' skepticism might indicate that it was the ***district court's*** reading of Mori that was wrong.

This is what the objective indicia, when properly considered, are intended to do—to serve as a check on hindsight by preventing the court from "read[ing] into the prior art the teachings of the invention in issue." *Apple*, 839 F. 3d at 1052. Indeed, ***all*** skepticism of a proven invention appears incorrect in hindsight, which is why it is the fact of contemporaneous skepticism, and not an after-the-fact judgment of its wisdom, that is properly weighed against obviousness. "Expressions of disbelief by experts constitute strong evidence of nonobviousness." *Envtl. Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 697–98 (Fed. Cir. 1983) (citing *Adams*, 383 U.S. at 52).

Moreover, to the extent the district court found that the experts were not aware of Mori's results, this finding is both implausible and clearly wrong. It is implausible because the notes refer to "***this*** group of patients," i.e., the population of severe hypertriglyceridemic patients, not those with mild dyslipidemia as in Mori. And it is clearly wrong because the participants did know about Mori. An additional set of

contemporaneous notes refers to Mori (Appx91278–91284 at Appx91282), as does the invitation packet to the meeting (Appx43970; Appx43986; Appx43992; Appx44015–44019). Indeed, the invitation packet explicitly provided Mori's EPA results, as well as other prior art studies that tested EPA in patients without severe hypertriglyceridemia. (Appx43986; Appx43995; Appx44015–44020.)

Similarly, the district court also failed to give fair consideration to evidence as to how Amarin's patented treatment methods were "viewed in the marketplace, by those directly interested in the product." *See Kinetic Concepts*, 688 F.3d at 1370. As one would expect when a company solves a long-felt but unmet need, VASCEPA® received significant recognition. One prominent doctor recognized that VASCEPA® was a "real advance in the treatment of triglycerides" because "[i]t gives you all the benefits without the downside" and that Amarin's invention proved that "small companies [can still] do innovative things." (Appx86650; *see also* Appx48698–48706 at 48702.) Instead of considering what effect this contemporaneous praise had in an obviousness analysis, the district court was quick to write it off, erroneously characterizing the praise as "equivocal" because doctors initially expressed "caveats" about the early results of VASCEPA® because they had not yet been peer-reviewed. (Appx68; Appx42; *see also* Appx88649.) The court apparently did not consider the possibility that doctors were understandably wary of these surprising results because they were inconsistent with their prior understanding of the disease, and that their

hesitance to accept the surprising results was more likely simply further evidence of the skepticism Amarin's inventors faced in pursuing their inventions.

As to VASCEPA®'s unexpected lowering of Apo-B, the district court erred in brushing this aside based on Kurabayashi. While we address below in Section B the district court's error in relying on Kurabayashi as part of its prima facie case, the district court's only other basis for rejecting this unexpected result was its statement that the examiner, who cited Apo-B lowering as an unexpected result in allowing the claims, was not aware of Kurabayashi. (Appx62.) This is wrong, as Kurabayashi was before the examiner during prosecution and listed on the face of the patents-in-suit. (Appx79.)

Finally, as one would also expect when a company comes out with a much-needed new method of treating a life-threatening condition, VASCEPA® has enjoyed success in the marketplace. (Appx39–42.) As this Court has held, commercial success due to the merits of a patented invention is powerful evidence of non-obviousness. *See, e.g.*, *Leo Pharm.*, 726 F.3d at 1358; *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1325 (Fed. Cir. 1999). Yet again, the district court failed even to ask why, if this invention were so obvious, other, larger and much more well-funded companies than Amarin didn't seize upon the commercial opportunity. Instead, because it had already reached its conclusion, the district court perfunctorily stated in one line that commercial success "weighs in favor" of non-obviousness, without anything more. (Appx69.)

2. The District Court Legally Erred by Concluding Obviousness Before Considering Objective Indicia

Fundamentally, the district court arrived at the wrong answer because it asked the wrong question. The question the district court should have asked was whether the claims would have been obvious based on consideration of "***all*** evidence of obviousness and non-obviousness"—including evidence of objective indicia. *Cyclobenzaprine*, 676 F.3d at 1077 (emphasis in original). This is because objective indicia are not second-class citizens in the obviousness analysis—they "may often be the most probative and cogent evidence in the record." *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983); *see also Ortho-McNeil*, 520 F.3d at 1365. As such, "[a]ll evidence" including objective indicia evidence "must be considered *before* a conclusion on obviousness is reached." *Lindemann Maschinenfabrik GMBH v. Am. Hoist & Derrick Co.*, 730 F.2d 1452, 1461 (Fed. Cir. 1984) (emphasis in original).

This is not the question the district court answered. Instead of looking to ***all*** of the evidence before reaching a determination of obviousness, the district court first considered only an erroneous "prima facie" case of obviousness—namely the content of the prior art, the scope of the prior art, and the motivations and expectations of a skilled artisan. (*See* Appx57–61.) Based on the court's consideration of the "prima facie" obviousness case, but ***before*** considering any evidence of objective indicia, the Court determined that "defendants presented clear and convincing evidence at Trial that all Asserted Claims are invalid as obvious." (Appx57.) Then and only then did

the district court look to the objective indicia evidence, improperly shifting the burden of persuasion to Amarin, and asking whether the objective indicia evidence "overc[a]me the Court's finding that all Asserted claims are prima facie obvious." (Appx69.) *See ZUP, LLC v. Nash Mfg., Inc.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018) ("Our precedent is clear that the burden of persuasion remains with the challenger during litigation because every issued patent is entitled to a presumption of validity" even though "a patentee bears the burden of production with respect to evidence of secondary considerations").

To be sure, the district court paid lip service to this Court's precedents regarding secondary considerations—stating that they must be considered. (*See* Appx61.) But this Court's precedents explain that what matters is not only that evidence of objective indicia must be considered but ***how*** that evidence is considered. For example, in *Lindemann Maschinenfabrik*, this court found "error" where a district court first reached a "conclu[sion] that the claimed invention would have been obvious from the prior art" and then looked "only to see whether" the proffered evidence of objective indicia "was so overwhelming as to overcome that conclusion." 730 F.2d at 1461. And in *Cyclobenzaprine*, the Court found that "[t]he district court erred, however, by making its finding that the patents in suit were obvious before it considered the objective considerations." 676 F.3d at 1075; *see also Apple*, 839 F.3d at 1048 ("A determination of whether a patent claim is invalid as obvious under § 103 requires consideration of all four *Graham* factors, and it is error to reach a conclusion

of obviousness until all those factors are considered."). This is exactly the erroneous approach taken by the district court here. Instead of treating the objective indicia evidence as part of the core obviousness analysis, the district court relegated them to being a mere "afterthought." *Leo Pharm.*, 726 F.3d at 1358.

Amarin's complaint here is not just semantics. The powerful objective indicia evidence here lays Defendants' obviousness theory bare—revealing that under the clothes of what appears to be a simple-sounding obviousness theory lies nothing but hindsight. Yet, at each turn, the district court either discounted or minimized the objective indicia evidence because it had already reached a conclusion of obviousness. The result was a series of findings inconsistent with the record and each other. The district court found that VASCEPA® satisfied a long-felt but unmet need and was a commercial success, yet somehow received only "equivocal" praise. And experts' contemporaneous skepticism was rejected on the thinnest of reeds, in the face of evidence that should have caused the district court to give that skepticism more weight, not less.

None of this is to say that a district court commits error whenever it utters the words "prima facie case" in conducting an obviousness analysis. As this Court recognized in *Cyclobenzaprine*, this Court's precedents contain decisions using this terminology. *See* 676 F.3d at 1077. However, none of these cases sanction reaching a conclusion of obviousness before considering the objective indicia—"even panels that have used the 'prima facie' and 'rebuttal' language generally have made clear that a fact

finder must consider *all* evidence of obviousness and nonobviousness before reaching a determination." *Id.* But, ultimately, what matters is not the language the court uses but the mode of analysis, which here violated this Court's precedents requiring that all evidence actually be considered before a court decides obviousness.

3. The District Court Improperly Required Plaintiffs to Show Every Objective Indicia Raised Supported Non-Obviousness

In addition to improperly pitting objective indicia against a "prima facie" case of obviousness, the district court also legally erred by pitting the categories of objective indicia against each other. Specifically, the Court held that the objective indicia it found present were "outweighed by the fact that the Court found" other categories of objective indicia not present. (Appx69.) The district court did not cite any caselaw supporting this approach, because there is none.

To the contrary, this Court has specifically held that a lack of objective indicia "does not weigh in favor of obviousness." *Miles Labs, Inc. v. Shandon Inc.*, 997 F.2d 870, 878 (Fed. Cir. 1993) (citing *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955 (Fed. Cir. 1986)). Nor is there any reason why one of the objective indicia, such as commercial success, should be "outweighed" by the purported failure to prove another, such as praise. Following the district court's logic, Amarin would have been better off had it simply brought less evidence, because then there would have been fewer categories of objective indicia to count against those that the district court found. This cannot be the law.

This Court has repeatedly found that evidence regarding only a few objective indicia can still be strong evidence showing non-obviousness. *See, e.g.*, *Cyclobenzaprine*, 676 F.3d at 1080–84 (long-felt need and failure by others supported a conclusion of non-obviousness); *Millennium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1368–69 (Fed. Cir. 2017) (unexpected results and long-felt need supported a conclusion of non-obviousness); *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1346–48 (evidence of competitors licensing and industry praise warranted reversal of PTAB's conclusion of obviousness). Thus, even if the district court were correct that only two objective indicia favored plaintiffs—and it was not—there was no reason to devalue those two categories because Amarin did not succeed in proving other, unrelated objective indicia. This additional legal error further minimized the weight that the district court gave to objective indicia, and further warrants reversal.

B. Hindsight Bias Infected the Court's Motivation and Reasonable Expectation Analysis

"[T]he best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000). Linked to motivation is reasonable expectation of success, which also must be rigorously applied to avoid hindsight. *See, e.g.*, *OSI Pharm., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) (rejecting obviousness finding in part because

"[i]t is only with the benefit of hindsight that a person of skill in the art would have had a reasonable expectation of success in view of the asserted references").

The district court's analysis of both these concepts was anything but "rigorous." To prevail, Defendants had to show by ***clear and convincing evidence*** that a skilled artisan would have been motivated to modify the prior Lovaza® treatment to arrive at the claimed EPA-only regimen, and that she would have reasonably expected that doing so would not, like all the other approved treatments, dramatically raise LDL-C. The problem for Defendants, and the district court, is that there is nowhere near enough evidence in the record to meet that high burden, and the district court legally erred in concluding otherwise. Indeed, the only way the district court reached its conclusion was through legal and factual error that ignored the critical teachings in the art about the differential LDL-C effects of triglyceride-lowering agents in patients with and without severe hypertriglyceridemia, and which effectively required Amarin to prove its invention non-obvious, as opposed to Defendants proving the opposite. These errors require reversal.

1. The District Court Erred in Ignoring Defendants' Lack of Evidence on the Key Issue—the Effect of EPA-Only Treatments on LDL-C in Severe Hypertriglyceridemia Patients

Fundamentally, the court legally erred in concluding a skilled artisan would have found it obvious to change Lovaza®'s omega-3 mixture including DHA and EPA meant for one patient population—those with ***severe hypertriglyceridemia***—

based on references showing the use of pure EPA in a fundamentally different population—those with ***mild to moderately elevated triglycerides***, i.e., Mori, Hayashi, and Kurabayashi. This difference in patient populations is critical, because, as the record evidence made clear, skilled artisans understood patients with severe hypertriglyceridemia responded differently to triglyceride-lowering drugs because of their genetics than those with milder hypertriglyceridemia. (*See supra* Fact Section I.B.2; Appx47–48.) As the district court found, and the experts agreed, all prior art treatments for severe hypertriglyceridemia "***dramatically increase[d]*** LDL-C levels[.]" (Appx5; *see also* Appx2329–2333 (Toth); Appx2336-2344 (Toth); Appx43939–43940; Appx44323–44324; Appx887–890 (Budoff); Appx953 (Budoff); Appx1450–1451 (Heinecke); Appx1430–1431 (Heinecke); Appx47720.) Yet in patients with milder forms of hypertriglyceridemia, these same treatments actually ***lowered*** LDL-C levels or raised them only slightly, if at all. (*See supra* Fact Section I.B.3; Appx1474–1478 (Heinecke).)

In its opinion, the district court regrettably ignored this important difference between the patient populations that extensive record evidence demonstrates. (*See supra* Fact Sections I.B.3, III.) Because of this, the court's analysis did not grapple with the fundamental problem at the heart of Defendants' case: that Mori and the rest of the prior art taught ***nothing*** about LDL-C effects in severe hypertriglyceridemia patients. As Dr. Heinecke admitted, before Amarin's invention, ***no one knew*** how EPA alone would work in severe hypertriglyceridemia patients:

> I don't think there's ***any evidence*** in the prior literature about what the impact of EPA would be on LDL cholesterol in patients with triglycerides above 500 milligrams per deciliter.

(Appx1398–1399 at 800:2–5; *see also id.* at 799:9–11 ("I'm not arguing here that we know what the impact is of EPA on LDL cholesterol levels above 500 milligrams per deciliter.").)

Without such a teaching, Defendants did not show that a skilled artisan would have had reason to modify Lovaza® to create a pure EPA treatment based on the prior art, or that she would have had a reasonable expectation that pure EPA would somehow behave differently than every other approved treatment for severe hypertriglyceridemia. *See Millennium Pharm.*, 862 F.3d at 1365–66 (motivation to combine erroneous where "no reference suggest[ed]" making the claimed modification to improve stability and "undisputed facts" were to the contrary); *Cyclobenzaprine*, 676 F.3d at 1070 ("While it may have been obvious to experiment with the use of the same PK profile when contemplating an extended-release formulation, there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective.").

The district court's finding otherwise begins with a hindsight-based premise and ends with a faulty conclusion: 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." (Appx57.) But

Defendants never showed that a skilled artisan, looking at Lovaza®'s LDL-C effects, would have assumed that either EPA or DHA (or both) were the cause of the LDL-C increase or that removing one of them would in any way help. Instead, the evidence showed that skilled artisans believed that LDL-C increases resulted from the increased conversion of VLDL to LDL—in other words, that they were an unfortunate but inevitable result of all approved triglyceride-lowering drugs in this patient population. (Appx107777–107783; Appx47720; Appx2344–2352 (Toth); Appx2460 (Toth); Appx48848; Appx44256–44258; Appx48910–48911; Appx43935–43936.)[7]

In this regard, Dr. Heinecke never presented the district court with any alternative mechanism for the known differential LDL-C effects that was accepted in the art. Instead, he "imagined" different mechanisms. (Appx1457–1458.) And as for the prior art that discussed the accepted mechanism, his basis for criticizing it was to quibble with the verbiage of prior art articles like McKenney (Appx1471) and obstinately disagree with statements from the FDA on, for example, the label of Tricor®. (Appx43935–43936; Appx1480–1482 (Heinecke); *see also* Appx43686; Appx1462–1463 (Heinecke).) Such unsupported expert testimony does not provide clear and convincing evidence of obviousness. *See ActiveVideo Networks, Inc. v. Verizon*

[7] Indeed, the Carlson reference called this a "general phenomenon" as far back as 1977. (Appx107779.) Without any citation, the district court rejected Carlson as not reflecting what a skilled artisan would believe in 2008 because it was from 1977. (Appx60.) Given that all experts and the district court agreed that niacin, and all other approved treatments for severe hypertriglyceridemia before the invention, raised LDL-C, this was clear error.

Commc'ns, Inc., 694 F.3d 1312, 1327 (Fed. Cir. 2012); *Innogenetics N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008).

The district court's citation of Dr. Toth's agreement 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" also provides no support to Defendants' case. (Appx57; Appx2580–2583 at 1787:6–10 (Toth).) Notably, the district court's excerpt omits Dr. Toth's response to the preceding question. When first asked whether it would have been obvious to consider whether Lovaza's LDL-C effects were due to only one of Lovaza®'s constituents, Dr. Toth answered "[n]ot in patients with severe hypertriglyceridemia." (Appx2580–2581 at 1786:23–1787:2.) This is in line with Dr. Toth's extensive testimony that ordinary artisans understood that it was not the specific treatments that caused the LDL-C increases, but rather the condition itself. (*See* Appx2344–2352.)

Even crediting the district court's parsing of Dr. Toth's testimony, however, it shows only that a skilled artisan may have had reason to investigate the extent by which DHA and EPA might increase LDL-C in the severely hypertriglyceridemic population. But a reason to investigate is not enough to provide either the motivation to remove entirely all of the constituents of Lovaza® save one, or the reasonable expectation that doing so would prevent LDL-C increases, ***particularly where the prior art was conceded not to address what would happen if such an investigation was undertaken***. *See Sanofi Synthelabo v. Apotex, Inc.*, 550 F.3d 1075,

1088 (Fed. Cir. 2008) (rejecting obviousness of selection of one of two enantiomers as based on "hindsight knowledge" of the "desirable properties" of the chosen enantiomer); *Leo Pharm.*, 726 F.3d at 1356 (finding the claimed invention would not be "obvious to try" simply because a skilled artisan "would have been capable of selecting the correct formulation from available alternatives").

Second, the district court erred in concluding that the EPA-only references Mori, Hayashi, and Kurabayashi filled this gap, when it was undisputed that none of these references were directed to the relevant patient population, i.e., severe hypertriglyceridemia. (Appx24–30; Appx57–60.) On Mori, Dr. Heinecke admitted that the patients tested did not have "even high triglycerides, let alone very high triglycerides[.]" (Appx1495.) On Kurabayashi, he admitted that the "upper limit on triglycerides" was 400 mg/dL, and that the patients did not have severe hypertriglyceridemia. (Appx1495–1497.) And on Hayashi, Dr. Heinecke admitted that, even if there may have been 1 or 2 patients with levels above 500, "they were not measuring LDL-C values for patients over 500" and "Hayashi is ***not telling us anything*** about the effect of EPA on LDL-C values in severely hypertriglyceridemic patients[.]" (Appx1492–1494.) The district court's finding that "Mori, Hayashi, and Kurabaysahi disclosed that EPA did not increase LDL-C" (Appx58) is, at best, incomplete, in light of these admissions. For the same reason, the court's finding that Kurabayashi taught that EPA reduced Apo-B levels (Appx58; Appx66) is flawed because Kurabayashi was in the wrong population of patients—patients with ***normal***

average triglycerides (around 135 mg/dL)—not patients with severe hypertriglyceridemia. (Appx88401–88403.)

The district court also erroneously rejected Dr. Toth's testimony that "all [prior art] treatments increased LDL-C in patients with very high triglycerides," concluding "that cannot be correct, because Mori taught that EPA did not increase LDL-C levels like DHA did." (Appx59.) But, the district court itself recognized that, before Dr. Manku's invention, prior art "treatments for severe hypertriglyceridemia ***dramatically increase[d]*** LDL-C levels[.]" (Appx5.) And, again, it never explained why Mori (or any of the other EPA-only references) are even applicable to ***severe hypertriglyceridemia patients***—patients who, as discussed above, were understood to respond differently to triglyceride-lowering drugs because of their genetics. Without a link to those severe hypertriglyceridemia patients, there can be no obviousness. *See Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1272–73 (Fed. Cir. 2018) (reversing obviousness determination where defendant conceded that no prior art taught claimed use of citric acid and failed to present "clear and convincing evidence of a teaching or suggestion to use citric acid particles as a carrier . . . or that the actual beneficial results would be obtained").

The primary rationale for the district court's application of Mori-type prior art to severe hypertriglyceridemia patients appears to have been its finding that Amarin's argument that those patients respond differently to triglyceride-lowering drugs than non-severe hypertriglyceridemia patients "lack[ed] evidentiary support[.]" (Appx60.)

Yet all the court relied on for this conclusion was Dr. Toth's unremarkable testimony that drugs that lower triglycerides in the non-severe patient population also lower triglycerides in the severe patient population. (Appx60.) Amarin never disputed this, and it is irrelevant to the critical question, on which Defendants bore the burden of proof: whether triglyceride-lowering drugs cause different effects ***on LDL-C*** in the different patient populations. And on that question, as explained above, the overwhelming evidence showed a distinct difference—one which would have ***dissuaded*** a skilled artisan from relying on Mori to modify Lovaza®'s treatment for severe hypertriglyceridemia patients. The district erred by ignoring this key evidence. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1579–80 (Fed. Cir. 1987) (rejecting the district court's factual findings as clearly erroneous where the court relied on hindsight and failed to reconcile differences between the prior art and the claimed invention); *Cyclobenzaprine*, 676 F.3d at 1073–75.

Amarin's internal documents, on which Defendants heavily relied at trial and the district court credited—say nothing different. (*See* Appx31; Appx675–715 (Ketchum); Appx719–726 (Ketchum); Appx90245–90269; Appx90286–90296; Appx90297–90417; Appx90418-90431.) That these documents characterized some of the prior art, including Mori, as showing that EPA was "LDL-neutral," does not change the critical and undisputed fact that Mori is only concerned with patients with mildly elevated triglycerides, not severe hypertriglyceridemia as required by the claims, which the documents note. (*See e.g.*, Appx90257 (noting Mori concerned baseline

triglycerides of less than 200 mg/dL); Appx90364–90365 (noting Mori concerned baseline triglycerides of less than 200 mg/dL and that none of the studies assessing EPA "recruited patients with severe hypertriglyceridemia"); Appx90428; *see also* Appx90288–90289.)

Nor do these documents show that Amarin's inventors, who had access to a wealth of additional clinical information on EPA on which to base their insights, merely did what the prior art taught, as Defendants claimed. "[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000); 35 U.S.C. § 103(a) (2011); *see also Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight."). That the inventors unsurprisingly were aware of Mori as just one of many "bits and pieces" to the puzzle cannot show, by clear and convincing evidence, that a skilled artisan would have found it obvious to modify Lovaza® based on Mori. As noted above, experts provided with information about Mori's results at the relevant time still believed that EPA would raise LDL-C in severe hypertriglyceridemia patients. (Appx47720; *see supra* Fact Section I.B.1.)

Finally, the district court's citation of the examiner's initial finding of obviousness that the applicants later overcame was also legal error. (Appx59; Appx57815–57822.) Almost every patent ever allowed was once rejected by an examiner. That the examiner initially found a prima facie case to use EPA to lower

triglycerides in severe hypertriglyceridemia patients during prosecution does not provide any evidence, let alone clear and convincing evidence, to show obviousness after the patent has issued, and is presumed valid. *See* 35 U.S.C. § 282; *Quad Envtl. Techs. Corp. v. Unions Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991) (emphasizing that obviousness determinations are made by the courts "without deference to the rulings of the patent examiner").

2. The District Court Improperly Shifted the Burden to Amarin to Prove Non-Obviousness and then Erred in Ignoring the Evidence Amarin Presented

Without clear and convincing evidence in the record, the only way the Court reached its obviousness conclusion was by shifting the burden to Amarin to show non-obviousness. Instead of requiring Defendants to show that a skilled artisan would have reasonably expected Mori's findings to be applicable to severe hypertriglyceridemia patients, the district court improperly required ***Amarin*** to show the opposite:

> 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.

(Appx60.) This is legally improper and contrary to the burden of proof on invalidity, which always rests with the challenger. *See, e.g.*, *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015) (finding error where district court "concluded that these

claims were obvious because [the patentee] did not explain why the additional limitations rendered the claims non-obvious").

The court's conclusion also constituted factual error because it was directly contradicted by the trial record.[8] Dr. Toth cited ***extensive evidence*** that patients with triglycerides of at least 500 mg/dL experience an increase in LDL-C with triglyceride-lowering drugs because of genetic predispositions not shared by patients with triglycerides under 500 mg/dL. (*See supra* Fact Section I.B.2; Appx2325–2326 (Toth); Appx2329–2332 (Toth); Appx2336-2344 (Toth); Appx43939–43940; Appx44323–44324.) It is irrelevant that Dr. Toth stated the 500 mg/dL level "***was not set***" because of this differential LDL-C effect. (Appx60.) It does not matter ***why*** the 500 mg/dL demarcation was set; what matters is the known effects on LDL-C for patients with triglycerides at or above that level. And Dr. Toth's testimony was clear that "[t]he 500 threshold does, in fact, identify another group of patients who responds ***very differently*** to triglyceride-lowering medications in terms of their LDL increases." (Appx2653-2654 at 1859:22-1860:2.)

Similarly, the district court's reliance on Dr. Heinecke's testimony is, charitably, incomplete. *See Cyclobenzaprine*, 676 F.3d at 1073–74 (finding error where district court

[8] As noted above, the district court copied this entire passage from Defendants' proposed findings. Given its conclusory nature, the Court should have great concern about the weight given to these findings. *See, e.g. U.S. v. El Paso Nat. Gas Co.,* 376 U.S. 651, 656 (1964) (findings "drawn with the insight of a disinterested mind are, however, more helpful to the appellate court.").

relied on one portion of a witness's testimony but ignored other portions). Immediately after saying there is no "magical mechanistic difference" between triglyceride levels of 400, 500, and 600 mg/dL, which was cited by the district court, Dr. Heinecke admitted:

> The concern with pancreatitis is when one actually gets up above the 1000-milligram per deciliter, and this was something that was not well understood back in 2008. We knew that ***somewhere above 500 milligrams per deciliter the system for clearing triglycerides jams up. But no one knew what that level was***, but, we knew it was above 500 milligrams per deciliter."

(Appx1395–1396 at 796:17–797:2.) Dr. Heinecke's testimony is thus consistent with Dr. Toth's—before Amarin's invention, a skilled artisan would have understood that patients with triglyceride levels above 500 mg/dL ***do*** metabolize triglyceride-lowering drugs differently than those with levels below 500 mg/dL.

Likewise, Dr. Heinecke's general statement that "[q]ualitatively, [the effects of medications] tend to be the same" regardless of baseline triglyceride levels, which the district court credited, is insufficient to show that an ordinary artisan would understand that the ***LDL-C effects*** would be the same. (Appx1396 at 797:16–18.) This is particularly so given that, as the evidence elided by the district court shows, the very problem with severe hypertriglyceridemia was that the LDL-C effects were known ***not*** to be the same in patients who have very high baseline triglycerides compared to others. (Appx60–61; Appx1396 (Heinecke); *see, e.g.*, Appx1475–1478 (Heinecke).) Indeed, this was why there was a long-felt need. The district court's

apparent conclusion that baseline triglyceride levels do not matter in relation to LDL-C levels has no actual support in the record.

Finally, to the extent the district court's decision is based on its determination that Hayashi included "at least one patient with triglyceride levels > 500 mg/dL" and "does not limit its conclusion regarding EPA's effects on LDL-C levels to patients with lower triglyceride levels," this is also error. (Appx26–28.) Dr. Heinecke admitted that "they were not measuring LDL-C values" for any patient above 500 and that "Hayashi is ***not telling us anything*** about the effect of EPA on LDL-C values in severely hypertriglyceridemic patients[.]" (Appx1492–1494.) There is thus no evidence or data to expand Hayashi's teachings to patients with severe hypertriglyceridemia. The court's finding that the teachings were "not limited" to patients with lower triglycerides is yet another example of legally improper burden shifting and is also clearly erroneous.

At bottom, the court's obviousness determination requires skilled artisans to throw out what they knew about approved treatments for severe hypertriglyceridemia and conclude that, based on studies in patients ***without*** that condition, EPA was likely to behave differently than every other approved treatment for the disease. But a person of ordinary skill is "presumed to be one who thinks along the line of conventional wisdom in the art," *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985), not one who ignores the teachings of that art to reach different conclusions. The district court's obviousness judgment substitutes its

hindsight views of the prior art for the ordinary artisan's. That judgment should be reversed.

CONCLUSION

For the reasons above, the Court should reverse the district court's finding that the asserted claims are obvious.

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Respectfully submitted,

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ADDENDUM

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.

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.

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)

	VASCEPA 4 g/day N=76		Placebo N=75		Difference (95% Confidence
Parameter	Baseline	% Change	Baseline	% Change	Interval)
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:

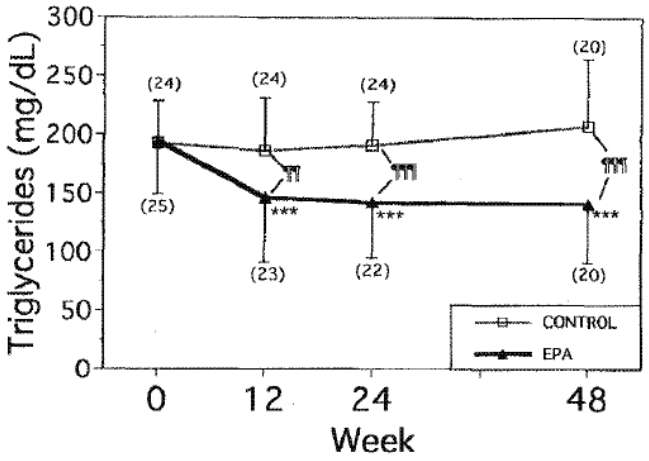

Figure 2. Changes in serum triglycerides levels from baseline to week 48 in the control and eicosapentaenoic acid groups in women whose level of triglycerides was not less than 150 mg/dL at baseline. Abbreviations as in Figure 1. Data are mean ± standard deviation. Numbers in parentheses indicate number 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

AO450 (NVD Rev. 2/18) Judgment in a Civil Case

UNITED STATES DISTRICT COURT

DISTRICT OF NEVADA

AMRIN PHARMA, INC., *et al.*,

Plaintiffs,

v.

HIKMA PHARMACEUTICALS USA, INC., *et al.*,

Defendants.

JUDGMENT IN A CIVIL CASE

Case No. 2:16-cv-2525-MMD-NJK

___ **Jury Verdict.** This action came before the Court for a trial by jury. The issues have been tried and the jury has rendered its verdict.

___ **Decision by Court.** This action came to trial or hearing before the Court. The issues have been tried or heard and a decision has been rendered.

X **Decision by Court.** This action came for consideration before the Court. The issues have been considered and a decision has been rendered.

IT IS ORDERED AND ADJUDGED 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.

IT IS FURTHER ORDERED that judgment is hereby entered in favor of Defendants on Plaintiffs' claim and on Defendants' counterclaims, and this case is closed.

Date: March 30, 2020

CLERK OF COURT

Signature of Clerk or Deputy Clerk

U 7533787

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 04, 2015

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *8,293,728*
ISSUE DATE: *October 23, 2012*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

JOHN A BURSON
Certifying Officer

PLAINTIFFS' EXHIBIT
PX 0021
Civil Action No.
2:16-cv-02525-MMD-NJK

AMRN-PEXP-0000001


US008293728B2

(12) **United States Patent**
Manku et al.

(10) **Patent No.: US 8,293,728 B2**
(45) **Date of Patent: *Oct. 23, 2012**

(54) **METHODS OF TREATING HYPERTRIGLYCERIDEMIA**

(75) Inventors: **Mehar Manku**, England (GB); **Ian Osterloh**, Kent (GB); **Pierre Wicker**, Mystic, CT (US); **Rene Braeckman**, Richboro, PA (US); **Paresh Soni**, Mystic, CT (US)

(73) Assignee: **Amarin Pharmaceuticals Ireland Limited**, Dublin (IE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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(60) Provisional application No. 61/151,291, filed on Feb. 10, 2009, provisional application No. 61/173,755, filed on Apr. 29, 2009.

(51) **Int. Cl.**

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

19 Claims, No Drawings

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METHODS OF TREATING HYPERTRIGLYCERIDEMIA

This application is a continuation of co-pending U.S. application Ser. No. 12/702,889 filed on Feb. 2, 2010 which claims priority to U.S. provisional application Ser. No. 61/151,291 filed Feb. 10, 2009 and U.S. provisional application Ser. No. 61/173,755 filed Apr. 29, 2009, each of which are incorporated by reference herein in their entireties.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof In one embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

In another embodiment, the invention provides a method of treating moderate to severe hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention,

and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/dl, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/dl, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

In one embodiment, the subject or subject group being treated in accordance with methods of the invention has pre-

viously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline;

(b) reduced Apo B levels compared to baseline;

(c) increased HDL-C levels compared to baseline;

(d) no increase in LDL-C levels compared to baseline;

(e) a reduction in LDL-C levels compared to baseline;

(f) a reduction in non-HDL-C levels compared to baseline;

(g) a reduction in vLDL levels compared to baseline;

(h) an increase in apo A-I levels compared to baseline;

(i) an increase in apo A-I/apo B ratio compared to baseline;

(j) a reduction in lipoprotein A levels compared to baseline;

(k) a reduction in LDL particle number compared to baseline;

(l) an increase in LDL size compared to baseline;

(m) a reduction in remnant-like particle cholesterol compared to baseline;

(n) a reduction in oxidized LDL compared to baseline;

(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;

(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;

(q) a reduction in homeostasis model insulin resistance compared to baseline;

(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;

(s) a reduction in intracellular adhesion molecule-1 compared to baseline;

(t) a reduction in interleukin-6 compared to baseline;

(u) a reduction in plasminogen activator inhibitor-1 compared to baseline;

(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;

(w) an increase in serum or plasma EPA compared to baseline;

(x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or

(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n-3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no or no increase in RBC DHA.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking an additional measurement of said one or more markers.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10

weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a)-(y) described immediately above.

In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least

about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 26 or more of outcomes (a)-(y) described immediately above.

Parameters (a)-(y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6^{th} Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (e.g. greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg,

about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In another embodiment, the EPA comprises In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In another embodiment, the invention provides use of any composition described herein for treating moderate to severe

hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder.

EXAMPLES

A multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≧500 mg/dL. The primary objective of the study is to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≧16.94 mmol/L).

The secondary objectives of this study are the following:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid and apolipoprotein profiles;
3. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
4. To determine the effect of AMR101 on oxidized LDL;
5. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
6. To determine the effect of AMR101 on insulin resistance;
7. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
8. To determine the effects of AMR101 2 g daily and 4 g daily on the incorporation of fatty acids into red blood cell membranes and into plasma phospholipids;
9. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
10. To explore the relationship between an increase in red blood cell membrane eicosapentaenoic acid (EPA) concentrations and the reduction in fasting TG levels.

The population for this study is men and women (women of childbearing potential will need to be on contraception or practice abstinence) >18 years of age with a body mass index ≦45 kg/m^2 who are not on lipid-altering therapy or are currently on lipid-altering therapy. Patients currently on statin therapy (with or without ezetimibe) will be evaluated by the investigator as to whether this therapy can be safely discontinued at screening, or if it should be continued. If statin therapy (with or without ezetimibe) is to be continued, dose(s) must be stable for ≧4 weeks prior to randomization. Patients taking non-statin, lipid-altering medications (niacin >200 mg/day, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), must be able to safely discontinue non-statin, lipid-altering therapy at screening.

Approximately 240 patients will be randomized at approximately 50 centers in North America, South America, Central America, Europe, India, and South Africa. The study will be a 58- to 60-week, Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, double-blind, randomized, placebo-controlled treatment period; and (3) A 40-week, open-label, extension period.

During the screening period and double-blind treatment period, all visits are to be within ±3 days of the scheduled time. During the open-label extension period, all visits are to be within ±7 days of the scheduled time. The screening period includes a 4- or 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. s) must be stable for weeks prior to randomization.

The screening visit (Visit 1) will occur for all patients at either 6 weeks (for patients not on lipid-altering therapy at screening or for patients who will not need to discontinue their current lipid-altering therapy) or 8 weeks (for patients who will require washout of their current lipid-altering therapy at screening) before randomization, as follows:

Patients who do not require a washout: The screening visit will occur at Visit 1 (Week-6). Eligible patients will enter a 4-week diet and lifestyle stabilization period. At the screening visit, all patients will receive counseling regarding the importance of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet. Patients who will require a washout: The screening visit will occur at Visit 1 (Week-8). Eligible patients will begin a 6-week washout period at the screening visit. Patients will receive counseling regarding the NCEP TLC diet and will receive instructions on how to follow this diet. Site personnel will contact patients who do not qualify for participation based on screening laboratory test results to instruct them to resume their prior lipid-altering medications.

At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients will enter the 2-week TG qualifying period and will have their fasting TG level measured at Visit 2 (Week-2) and Visit 3 (Week-1). Eligible patients must have an average fasting TG level ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L) to enter the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit 2 (Week-2) and Visit 3 (Week-1) values. If a patient's average TG level from Visit 2 and Visit 3 falls outside the required range for entry into the study, an additional sample for fasting TG measurement can be collected 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study will be based on the average (arithmetic mean) of the values from Visit 3 and Visit 3.1.

After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients will be randomly assigned to 1 of the following treatment groups:

AMR101 2 g daily,
AMR101 4 g daily, or
Placebo.

During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-I/apo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurs, Visit 3.1) measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide 90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p<0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

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.

2. The method of claim **1**, wherein the pharmaceutical composition is administered to the subject 1 to 4 times per day.

3. The method of claim 2 wherein, the pharmaceutical composition is present in one or more capsules.

4. The method of claim 1, wherein the subject and the second subject have one or more of: a baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

5. The method of claim 4, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of 12 weeks to effect a reduction in fasting non-HDL-C and a reduction in fasting VLDL-C compared to the second subject.

6. The method of claim 4, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of 12 weeks to effect a reduction in fasting triglycerides of at least about 25% compared to the second subject.

7. The method of claim 4, comprising administering to the subject about 4 g of said pharmaceutical composition daily for the period of 12 weeks, to effect a reduction in fasting Lp-PLA2 of at least 10% compared to the second subject.

8. 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 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 fasting triglycerides of at least about 15% without substantially increasing LDL-C compared to a second subject having fasting triglyceride of 500 mg/dl to about 1500 who has not received the pharmaceutical composition and concurrent lipid altering therapy.

9. The method of claim 8, wherein the pharmaceutical composition is administered to the subject 1 to 4 times per day.

10. The method of claim 9, wherein the pharmaceutical composition is present in one or more capsules.

11. The method of claim 8, wherein the subject and the second subject have one or more of: a baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a baseline total cholesterol of about 250 mg/dl to about 300 mg/dl, a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

12. The method of claim 11, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of 12 weeks to effect a reduction in fasting non-HDL-C and a reduction in fasting VLDL-C compared to the second subject.

13. The method of claim 8, comprising administering to the subject about 4 g of the pharmaceutical composition daily for the period of 12 weeks to effect a reduction in fasting triglycerides of at least about 25%.

14. The method of claim 11, comprising:

administering to the subject about 4 g of the pharmaceutical composition daily for the period of 12 weeks to effect a reduction in fasting Lp-PLA2 of at least 10% compared to the second subject.

15. The method of claim 1, wherein the subject and the second subject consume a Western diet.

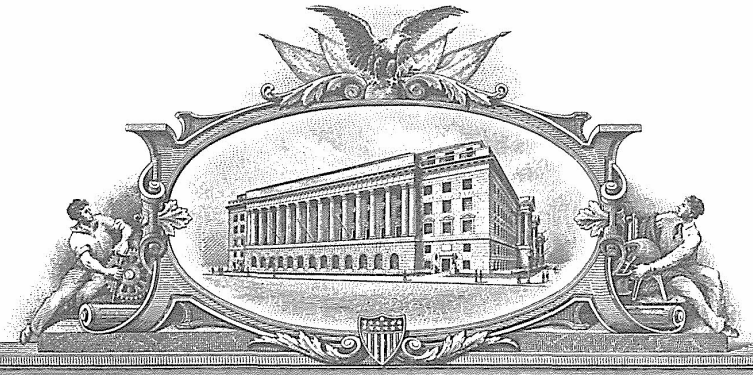
16. The method of claim 1, wherein no fatty acid of the pharmaceutical composition, except for ethyl-EPA, comprises more than about 0.6% by weight of all fatty acids combined.

17. The method of claim 8, wherein the subject and the second subject consume a Western diet.

18. The method of claim 8, 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.

19. A method of lowering triglycerides in a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy 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 12 weeks that is effective to reduce in a first patient population receiving 4 g per day of said composition without concurrent lipid altering therapy and having said baseline triglyceride level, a median triglyceride level by at least 5% without substantially increasing LDL-C, compared to a median triglyceride level and LDL-C level observed in a second patient population having said baseline triglyceride level who has not received the pharmaceutical composition and concurrent lipid altering therapy.

* * * * *



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ISSUE DATE: *November 27, 2012*

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Manku et al.

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(54) **METHODS OF TREATING HYPERTRIGLYCERIDEMIA**

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A61K 31/33	(2006.01)
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A61K 9/48	(2006.01)

(52) **U.S. Cl.** **514/183**; 514/549; 424/451

(58) **Field of Classification Search** 514/183, 514/549; 424/451

See application file for complete search history.

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

19 Claims, No Drawings

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METHODS OF TREATING HYPERTRIGLYCERIDEMIA

This application is a continuation of U.S. Ser. No. 12/702,889, filed Feb. 9, 2010, and claims priority to U.S. provisional application Ser. No. 61/151,291 filed Feb. 10, 2009 and U.S. provisional application Ser. No. 61/173,755 filed Apr. 29, 2009, each of which are incorporated by reference herein in their entireties.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof. In one embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

In another embodiment, the invention provides a method of treating moderate to severe hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention,

and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/dl, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/dl, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

In one embodiment, the subject or subject group being treated in accordance with methods of the invention has pre-

viously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about Ito about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about Ito about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline;

(b) reduced Apo B levels compared to baseline;

(c) increased HDL-C levels compared to baseline;

(d) no increase in LDL-C levels compared to baseline;

(e) a reduction in LDL-C levels compared to baseline;

(f) a reduction in non-HDL-C levels compared to baseline;

(g) a reduction in vLDL levels compared to baseline;

(h) an increase in apo A-I levels compared to baseline;

(i) an increase in apo A-I/apo B ratio compared to baseline;

(j) a reduction in lipoprotein A levels compared to baseline;

(k) a reduction in LDL particle number compared to baseline;

(l) an increase in LDL size compared to baseline;

(m) a reduction in remnant-like particle cholesterol compared to baseline;

(n) a reduction in oxidized LDL compared to baseline;

(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;

(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;

(q) a reduction in homeostasis model insulin resistance compared to baseline;

(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;

(s) a reduction in intracellular adhesion molecule-1 compared to baseline;

(t) a reduction in interleukin-6 compared to baseline;

(u) a reduction in plasminogen activator inhibitor-1 compared to baseline;

(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;

(w) an increase in serum or plasma EPA compared to baseline;

(x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or

(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n-3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no or no increase in RBC DHA.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking an additional measurement of said one or more markers.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10

weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a)-(y) described immediately above.

In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least

about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 26 or more of outcomes (a)-(y) described immediately above.

Parameters (a)-(y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6^{th} Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (e.g. greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg,

about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In another embodiment, the EPA comprises In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In another embodiment, the invention provides use of any composition described herein for treating moderate to severe

hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5 -10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder.

EXAMPLES

A multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≧500 mg/dL. The primary objective of the study is to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L).

The secondary objectives of this study are the following:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid and apolipoprotein profiles;
3. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
4. To determine the effect of AMR101 on oxidized LDL;
5. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
6. To determine the effect of AMR101 on insulin resistance;
7. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
8. To determine the effects of AMR101 2 g daily and 4 g daily on the incorporation of fatty acids into red blood cell membranes and into plasma phospholipids;
9. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
10. To explore the relationship between an increase in red blood cell membrane eicosapentaenoic acid (EPA) concentrations and the reduction in fasting TG levels.

The population for this study is men and women (women of childbearing potential will need to be on contraception or practice abstinence) >18 years of age with a body mass index ≦45 kg/m^2 who are not on lipid-altering therapy or are currently on lipid-altering therapy. Patients currently on statin therapy (with or without ezetimibe) will be evaluated by the investigator as to whether this therapy can be safely discontinued at screening, or if it should be continued. If statin therapy (with or without ezetimibe) is to be continued, dose(s) must be stable for ≧4 weeks prior to randomization. Patients taking non-statin, lipid-altering medications (niacin >200 mg/day, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), must be able to safely discontinue non-statin, lipid-altering therapy at screening.

Approximately 240 patients will be randomized at approximately 50 centers in North America, South America, Central America, Europe, India, and South Africa. The study will be a 58- to 60-week, Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, double-blind, randomized, placebo-controlled treatment period; and (3) A 40-week, open-label, extension period.

During the screening period and double-blind treatment period, all visits are to be within ±3 days of the scheduled time. During the open-label extension period, all visits are to be within ±7 days of the scheduled time. The screening period includes a 4- or 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. s) must be stable for ≧4 weeks prior to randomization.

The screening visit (Visit 1) will occur for all patients at either 6 weeks (for patients not on lipid-altering therapy at screening or for patients who will not need to discontinue their current lipid-altering therapy) or 8 weeks (for patients who will require washout of their current lipid-altering therapy at screening) before randomization, as follows:

Patients who do not require a washout: The screening visit will occur at Visit 1 (Week −6). Eligible patients will enter a 4-week diet and lifestyle stabilization period. At the screening visit, all patients will receive counseling regarding the importance of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet. Patients who will require a washout: The screening visit will occur at Visit 1 (Week −8). Eligible patients will begin a 6-week washout period at the screening visit. Patients will receive counseling regarding the NCEP TLC diet and will receive instructions on how to follow this diet. Site personnel will contact patients who do not qualify for participation based on screening laboratory test results to instruct them to resume their prior lipid-altering medications.

At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients will enter the 2-week TG qualifying period and will have their fasting TG level measured at Visit 2 (Week −2) and Visit 3 (Week −1). Eligible patients must have an average fasting TG level ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L) to enter the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit 2 (Week −2) and Visit 3 (Week −1) values. If a patient's average TG level from Visit 2 and Visit 3 falls outside the required range for entry into the study, an additional sample for fasting TG measurement can be collected 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study will be based on the average (arithmetic mean) of the values from Visit 3 and Visit 3.1.

After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients will be randomly assigned to 1 of the following treatment groups:

AMR101 2 g daily,
AMR101 4 g daily, or
Placebo.

During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-I/apo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week −1] or if it occurs, Visit 3.1) measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide ≧90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p<0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

1. A method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a 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 reduction in triglycerides and apolipoprotein B in the subject compared to a triglyceride level and apolipoprotein B level in a second subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a concurrent lipid altering therapy, and who has not received the pharmaceutical composition.

2. The method of claim **1** wherein the composition is administered to the subject 1 to 4 times per day.

3. The method of claim 1 wherein the composition is present in one or more capsules.

4. The method of claim 1 comprising administering the composition to the subject daily for a period of 12 weeks to effect a reduction in apolipoprotein B and substantially no increase in LDL-C levels compared to the second subject.

5. The method of claim 1 comprising administering 4 g of the composition to the subject daily for a period of 12 weeks to effect at least a 5% reduction in triglyceride levels compared to a triglyceride level in the second subject.

6. The method of claim 1 comprising administering 4 g of the composition to the subject daily for a period of 12 weeks to effect at least a 5% reduction in VLDL-C levels compared to a VLDL-C level in the second subject.

7. The method of claim 1 comprising administering 4 g of the composition to the subject daily for a period of 12 weeks to effect a reduction in non-HDL-C levels compared to a non-HDL-C level in the second subject.

8. The method of claim 1 comprising administering 4 g of the composition to the subject daily for a period of 12 weeks to effect a reduction in triglycerides of at least about 25% and a reduction in non-HDL C of at least about 5% as compared to the second subject.

9. The method of claim 1 comprising administering 4 g of the composition to the subject daily for a period of 12 weeks to effect a reduction in Lp-PLA2 of at least about 15% as compared a Lp-PLA2 level in the second subject.

10. The method of claim 9 comprising administering 4 g of the composition to the subject daily for a period of 12 weeks to effect a reduction in total cholesterol of at least about 15% as compared a total cholesterol level in the second subject.

11. The method of claim 1 wherein the subject and the second subject consume a Western diet.

12. The method of claim 1 wherein the concomitant lipid-altering therapy is a statin.

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 a 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 LDL-C or apolipoprotein B in the subject.

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 in the subject.

15. The method of claim 13 wherein the subject and the second subject consume a Western diet.

16. The method of claim 13 wherein the concomitant lipid-altering therapy is a statin.

17. A method of reducing triglycerides and apolipoprotein B in a subject having a fasting baseline triglyceride level of 500 mg/dl to about 1500 mg/dl, who does not receive a 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 reduction in triglycerides and apolipoprotein B in the subject compared to a triglyceride level and an apolipoprotein B level at a baseline prior to initial administration of the pharmaceutical composition.

18. The method of claim 17 wherein the subject and the second subject consume a Western diet.

19. The method of claim 17 wherein the concomitant lipid-altering therapy is a statin.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 8,318,715 B2
APPLICATION NO. : 13/282145
DATED : November 27, 2012
INVENTOR(S) : Manku et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

Column 18, line 16, of Claim 14, should read, "...significant increase of LDL-C in the subject."

Column 18, lines 17-18, of Claim 15, should read, "The method of claim 13 wherein the subject consumes a Western Diet."

Signed and Sealed this
Eleventh Day of August, 2015

Michelle K. Lee

Michelle K. Lee
Director of the United States Patent and Trademark Office

U 7533787

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 04, 2015

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *8,357,677*
ISSUE DATE: *January 22, 2013*

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

SYLVIA HOLLEY
Certifying Officer

PLAINTIFFS' EXHIBIT
PX 0025
Civil Action No.
2:16-cv-02525-MMD-NJK

AMRN-PEXP-0000046


US008357677B1

(12) **United States Patent**
Manku et al.

(10) **Patent No.: US 8,357,677 B1**
(45) **Date of Patent: *Jan. 22, 2013**

(54) **METHODS OF TREATING HYPERTRIGLYCERIDEMIA**

(75) Inventors: **Mehar Manku**, England (GB); **Ian Osterloh**, Kent (GB); **Pierre Wicker**, Mystic, CT (US); **Rene Braeckman**, Richboro, PA (US); **Paresh Soni**, Mystic, CT (US)

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/608,775**

(22) Filed: **Sep. 10, 2012**

Related U.S. Application Data

(63) Continuation of application No. 13/349,153, filed on Jan. 12, 2012, now Pat. No. 8,293,728, which is a continuation of application No. 12/702,889, filed on Feb. 9, 2010, now Pat. No. 8,293,727.

(60) Provisional application No. 61/151,291, filed on Feb. 10, 2009, provisional application No. 61/173,755, filed on Apr. 29, 2009.

(51) **Int. Cl.**

A61K 9/48	(2006.01)
A61K 31/33	(2006.01)
A61K 31/02	(2006.01)
A01N 43/00	(2006.01)
A01N 37/06	(2006.01)

(52) **U.S. Cl.** **514/183**; 514/549; 514/451

(58) **Field of Classification Search** 514/183, 514/549, 451

See application file for complete search history.

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

9 Claims, No Drawings

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METHODS OF TREATING HYPERTRIGLYCERIDEMIA

This application is a continuation of co-pending U.S. application Ser. No. 13/349,153 filed on Jan. 12, 2012, which is a continuation of U.S. application Ser. No. 12/702,889 filed on Feb. 9, 2010 which claims priority to U.S. provisional application Ser. No. 61/151,291 filed Feb. 10, 2009 and U.S. provisional application Ser. No. 61/173,755 filed Apr. 29, 2009, each of which are incorporated by reference herein in their entireties.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof. In one embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

In another embodiment, the invention provides a method of treating moderate to severe hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/dl, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/dl, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

In one embodiment, the subject or subject group being treated in accordance with methods of the invention has previously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about Ito about 20 weeks, about Ito about 15 weeks, about 1 to about 12 weeks, about Ito about 10 weeks, about Ito about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline;
(b) reduced Apo B levels compared to baseline;
(c) increased HDL-C levels compared to baseline;
(d) no increase in LDL-C levels compared to baseline;
(e) a reduction in LDL-C levels compared to baseline;
(f) a reduction in non-HDL-C levels compared to baseline;
(g) a reduction in vLDL levels compared to baseline;
(h) an increase in apo A-I levels compared to baseline;
(i) an increase in apo A-I/apo B ratio compared to baseline;
(j) a reduction in lipoprotein A levels compared to baseline;
(k) a reduction in LDL particle number compared to baseline;
(l) an increase in LDL size compared to baseline;
(m) a reduction in remnant-like particle cholesterol compared to baseline;
(n) a reduction in oxidized LDL compared to baseline;
(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;
(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;
(q) a reduction in homeostasis model insulin resistance compared to baseline;
(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;
(s) a reduction in intracellular adhesion molecule-1 compared to baseline;
(t) a reduction in interleukin-6 compared to baseline;
(u) a reduction in plasminogen activator inhibitor-1 compared to baseline;
(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;
(w) an increase in serum or plasma EPA compared to baseline;
(x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or
(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n-3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no or no increase in RBC DHA.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking an additional measurement of said one or more markers.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about

1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a)-(y) described immediately above.

In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least

about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 26 or more of outcomes (a)-(y) described immediately above.

Parameters (a)-(y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6th Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (e.g. greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000

mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with meth-

ods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a

plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In another embodiment, the invention provides use of any composition described herein for treating moderate to severe hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder.

Examples

A multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≧500 mg/dL. The primary objective of the study is to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≧500 mg/dL and 1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L).

The secondary objectives of this study are the following:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid and apolipoprotein profiles;
3. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
4. To determine the effect of AMR101 on oxidized LDL;
5. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
6. To determine the effect of AMR101 on insulin resistance;
7. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
8. To determine the effects of AMR101 2 g daily and 4 g daily on the incorporation of fatty acids into red blood cell membranes and into plasma phospholipids;
9. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
10. To explore the relationship between an increase in red blood cell membrane eicosapentaenoic acid (EPA) concentrations and the reduction in fasting TG levels.

The population for this study is men and women (women of childbearing potential will need to be on contraception or practice abstinence) >18 years of age with a body mass index ≦45 kg/m^2 who are not on lipid-altering therapy or are currently on lipid-altering therapy. Patients currently on statin therapy (with or without ezetimibe) will be evaluated by the investigator as to whether this therapy can be safely discontinued at screening, or if it should be continued. If statin therapy (with or without ezetimibe) is to be continued, dose(s) must be stable for ≧4 weeks prior to randomization. Patients taking non-statin, lipid-altering medications (niacin >200 mg/day, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), must be able to safely discontinue non-statin, lipid-altering therapy at screening.

Approximately 240 patients will be randomized at approximately 50 centers in North America, South America, Central America, Europe, India, and South Africa. The study will be a 58- to 60-week, Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, double-blind, randomized, placebo-controlled treatment period; and (3) A 40-week, open-label, extension period.

During the screening period and double-blind treatment period, all visits are to be within ±3 days of the scheduled time. During the open-label extension period, all visits are to be within ±7 days of the scheduled time. The screening period includes a 4- or 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. s) must be stable for weeks prior to randomization.

The screening visit (Visit 1) will occur for all patients at either 6 weeks (for patients not on lipid-altering therapy at screening or for patients who will not need to discontinue their current lipid-altering therapy) or 8 weeks (for patients who will require washout of their current lipid-altering therapy at screening) before randomization, as follows:

Patients who do not require a washout: The screening visit will occur at Visit 1 (Week −6). Eligible patients will enter a 4-week diet and lifestyle stabilization period. At the screening visit, all patients will receive counseling regarding the importance of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet. Patients who will require a washout: The screening visit will occur at Visit 1 (Week −8). Eligible patients will begin a 6-week washout period at the screening visit. Patients will receive counseling regarding the NCEP TLC diet and will receive instructions on how to follow this diet. Site personnel will contact patients who do not qualify for participation based on screening laboratory test results to instruct them to resume their prior lipid-altering medications.

At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients will enter the 2-week TG qualifying period and will have their fasting TG level measured at Visit 2 (Week −2) and Visit 3 (Week −1). Eligible patients must have an average fasting TG level ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L) to enter the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit 2 (Week −2) and Visit 3 (Week −1) values. If a patient's average TG level from Visit 2 and Visit 3 falls outside the required range for entry into the study, an additional sample for fasting TG measurement can be collected 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study will be based on the average (arithmetic mean) of the values from Visit 3 and Visit 3.1.

After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients will be randomly assigned to 1 of the following treatment groups:

AMR101 2 g daily,
AMR101 4 g daily, or
Placebo.

During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-I/apo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week −1] or if it occurs, Visit 3.1) measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide ≧90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p<0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

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.

2. The method of claim **1**, wherein the pharmaceutical composition is administered to the subject 1 to 4 times per day.

3. The method of claim **2**, wherein the pharmaceutical composition is present in one or more capsules.

4. The method of claim 1, wherein the subject has a fasting baseline LDL-C from about 40 mg/dl to about 115 mg/dl.

5. The method of claim 1, wherein subject has one or more of: a median baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a median baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a median baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a median baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

6. 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 fasting triglycerides of at least about 10% without substantially increasing LDL-C compared to placebo control.

7. 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 fasting triglycerides of at least about 25% without substantially increasing LDL-C compared to placebo control.

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.

9. 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 VLDL-C compared to placebo control.

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June 04, 2015

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *8,367,652*
ISSUE DATE: *February 05, 2013*

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(12) **United States Patent**
Manku et al.

(10) **Patent No.: US 8,367,652 B2**
(45) **Date of Patent: *Feb. 5, 2013**

(54) **METHODS OF TREATING HYPERTRIGLYCERIDEMIA**

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This patent is subject to a terminal disclaimer.

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(52) **U.S. Cl.** **514/183**; 514/549; 514/451

(58) **Field of Classification Search** 514/183, 514/549, 451

See application file for complete search history.

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

18 Claims, No Drawings

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METHODS OF TREATING HYPERTRIGLYCERIDEMIA

This application is a continuation of co-pending U.S. application Ser. No. 13/349,153 filed on Jan. 12, 2012, which is a continuation of U.S. application Ser. No. 12/702,889 filed on Feb. 9, 2010 which claims priority to U.S. provisional application Ser. No. 61/151,291 filed Feb. 10, 2009 and U.S. provisional application Ser. No. 61/173,755 filed Apr. 29, 2009, each of which are incorporated by reference herein in their entireties.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof. In one embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

In another embodiment, the invention provides a method of treating moderate to severe hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/dl, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/dl, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

In one embodiment, the subject or subject group being treated in accordance with methods of the invention has previously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about Ito about 20 weeks, about Ito about 15 weeks, about 1 to about 12 weeks, about Ito about 10 weeks, about Ito about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline;
(b) reduced Apo B levels compared to baseline;
(c) increased HDL-C levels compared to baseline;
(d) no increase in LDL-C levels compared to baseline;
(e) a reduction in LDL-C levels compared to baseline;
(f) a reduction in non-HDL-C levels compared to baseline;
(g) a reduction in vLDL levels compared to baseline;
(h) an increase in apo A-I levels compared to baseline;
(i) an increase in apo A-I/apo B ratio compared to baseline;
(j) a reduction in lipoprotein A levels compared to baseline;
(k) a reduction in LDL particle number compared to baseline;
(l) an increase in LDL size compared to baseline;
(m) a reduction in remnant-like particle cholesterol compared to baseline;
(n) a reduction in oxidized LDL compared to baseline;
(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;
(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;
(q) a reduction in homeostasis model insulin resistance compared to baseline;
(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;
(s) a reduction in intracellular adhesion molecule-1 compared to baseline;
(t) a reduction in interleukin-6 compared to baseline;
(u) a reduction in plasminogen activator inhibitor-1 compared to baseline;
(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;
(w) an increase in serum or plasma EPA compared to baseline;
(x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or
(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n–3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no or no increase in RBC DHA.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking an additional measurement of said one or more markers.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about

1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a)-(y) described immediately above.

In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(h) an increase in apo A-Papo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least

about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 26 or more of outcomes (a)-(y) described immediately above.

Parameters (a)-(y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6th Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (e.g. greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000

mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with meth-

ods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a

plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In another embodiment, the invention provides use of any composition described herein for treating moderate to severe hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder.

EXAMPLES

A multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≧500 mg/dL. The primary objective of the study is to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L).

The secondary objectives of this study are the following:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid and apolipoprotein profiles;
3. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
4. To determine the effect of AMR101 on oxidized LDL;
5. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
6. To determine the effect of AMR101 on insulin resistance;
7. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
8. To determine the effects of AMR101 2 g daily and 4 g daily on the incorporation of fatty acids into red blood cell membranes and into plasma phospholipids;
9. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
10. To explore the relationship between an increase in red blood cell membrane eicosapentaenoic acid (EPA) concentrations and the reduction in fasting TG levels.

The population for this study is men and women (women of childbearing potential will need to be on contraception or practice abstinence)>18 years of age with a body mass index ≦45 kg/m^2 who are not on lipid-altering therapy or are currently on lipid-altering therapy. Patients currently on statin therapy (with or without ezetimibe) will be evaluated by the investigator as to whether this therapy can be safely discontinued at screening, or if it should be continued. If statin therapy (with or without ezetimibe) is to be continued, dose (s) must be stable for ≧4 weeks prior to randomization. Patients taking non-statin, lipid-altering medications (niacin >200 mg/day, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), must be able to safely discontinue non-statin, lipid-altering therapy at screening.

Approximately 240 patients will be randomized at approximately 50 centers in North America, South America, Central America, Europe, India, and South Africa. The study will be a 58- to 60-week, Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, double-blind, randomized, placebo-controlled treatment period; and (3) A 40-week, open-label, extension period.

During the screening period and double-blind treatment period, all visits are to be within ±3 days of the scheduled time. During the open-label extension period, all visits are to be within ±7 days of the scheduled time. The screening period includes a 4- or 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. s) must be stable for weeks prior to randomization.

The screening visit (Visit 1) will occur for all patients at either 6 weeks (for patients not on lipid-altering therapy at screening or for patients who will not need to discontinue their current lipid-altering therapy) or 8 weeks (for patients who will require washout of their current lipid-altering therapy at screening) before randomization, as follows:

Patients who do not require a washout: The screening visit will occur at Visit 1 (Week −6). Eligible patients will enter a 4-week diet and lifestyle stabilization period. At the screening visit, all patients will receive counseling regarding the importance of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet. Patients who will require a washout: The screening visit will occur at Visit 1 (Week −8). Eligible patients will begin a 6-week washout period at the screening visit. Patients will receive counseling regarding the NCEP TLC diet and will receive instructions on how to follow this diet. Site personnel will contact patients who do not qualify for participation based on screening laboratory test results to instruct them to resume their prior lipid-altering medications.

At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients will enter the 2-week TG qualifying period and will have their fasting TG level measured at Visit 2 (Week −2) and Visit 3 (Week −1). Eligible patients must have an average fasting TG level ≧500 mg/dL and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L) to enter the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit 2 (Week −2) and Visit 3 (Week −1) values. If a patient's average TG level from Visit 2 and Visit 3 falls outside the required range for entry into the study, an additional sample for fasting TG measurement can be collected 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study will be based on the average (arithmetic mean) of the values from Visit 3 and Visit 3.1.

After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients will be randomly assigned to 1 of the following treatment groups:

AMR101 2 g daily,
AMR101 4 g daily, or
Placebo.

During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-Papo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week −1] or if it occurs, Visit 3.1) measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide ≧90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p<0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

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.

2. The method of claim **1**, wherein the pharmaceutical composition is administered to the subject 1 to 4 times per day.

3. The method of claim **2**, wherein the pharmaceutical composition is present in one or more capsules.

4. The method of claim 1, wherein the subject has a fasting baseline LDL-C from about 40 mg/dl to about 115 mg/dl.

5. The method of claim 1, wherein subject has one or more of: a median baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a median baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a median baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a median baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

6. 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 fasting triglycerides of at least about 10% without substantially increasing LDL-C compared to baseline.

7. 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 fasting triglycerides of at least about 25% without substantially increasing LDL-C compared to baseline.

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 baseline.

9. 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 VLDL-C compared to baseline.

10. A method of lowering triglycerides in a subject having a fasting baseline triglyceride level of about 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, which when orally administered in a first patient population having said baseline triglyceride level and receiving, for a period of twelve weeks, 4 g per day of the pharmaceutical composition, is effective to reduce said baseline triglyceride level without substantially increasing LDL-C compared to a second patient population having said baseline triglyceride level that has not received the pharmaceutical composition.

11. The method of claim 10, wherein the pharmaceutical composition is administered to the subject 1 to 4 times per day.

12. The method of claim 11, wherein the pharmaceutical composition is present in one or more capsules.

13. The method of claim 10, wherein the subject has a fasting baseline LDL-C from about 40 mg/dl to about 115 mg/dl.

14. The method of claim 10, wherein subject has one or more of: a median baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a median baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a median baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a median baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

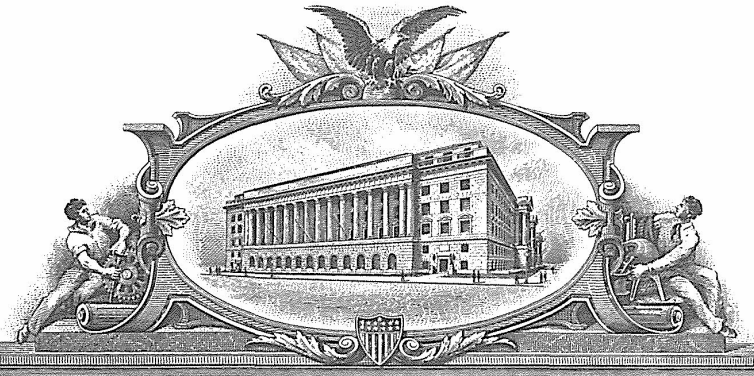
15. The method of claim 10, wherein the pharmaceutical composition, when orally administered daily to the first patient population for the period of twelve weeks is effective to reduce the baseline triglyceride level by at least about 10% without substantially increasing LDL-C compared to the second patient population that has not received the pharmaceutical composition.

16. The method of claim 10, wherein the pharmaceutical composition, when orally administered daily to the first patient population for the period of twelve weeks is effective to reduce the baseline triglyceride level by at least about 25% without substantially increasing LDL-C compared to the second patient population that has not received the pharmaceutical composition.

17. The method of claim 10, wherein the pharmaceutical composition, when orally administered daily to the first patient population for the period of twelve weeks is effective to reduce apolipoprotein B compared to the second patient population that has not received the pharmaceutical composition.

18. The method of claim 10, wherein the pharmaceutical composition, when orally administered daily to the first patient population for the period of twelve weeks is effective to reduce VLDL-C compared to the second patient population that has not received the pharmaceutical composition.

* * * * *



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U.S. PATENT: ***8,431,560***
ISSUE DATE: ***April 30, 2013***

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Manku et al.

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(54) **METHODS OF TREATING HYPERTRIGLYCERIDEMIA**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(63) Continuation of application No. 13/623,450, filed on Sep. 20, 2012, which is a continuation of application No. 13/349,153, filed on Jan. 12, 2012, now Pat. No. 8,293,728, which is a continuation of application No. 12/702,889, filed on Feb. 9, 2010, now Pat. No. 8,293,727.

(60) Provisional application No. 61/151,291, filed on Feb. 10, 2009, provisional application No. 61/173,755, filed on Apr. 29, 2009.

(51) **Int. Cl.**

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A61K 31/33	(2006.01)
A61K 31/02	(2006.01)
A01N 43/00	(2006.01)
A01N 37/06	(2006.01)

(52) **U.S. Cl.**
USPC **514/183**; 514/549; 424/451

(58) **Field of Classification Search** 514/183, 514/549; 424/451
See application file for complete search history.

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

20 Claims, No Drawings

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METHODS OF TREATING HYPERTRIGLYCERIDEMIA

This application is a continuation of co-pending U.S. application Ser. No. 13/623,450, filed on Sep. 20, 2012, which is a continuation of U.S. application Ser. No. 13/349,153 filed on Jan. 12, 2012, which is a continuation of U.S. application Ser. No. 12/702,889 filed on Feb. 9, 2010 which claims priority to U.S. provisional application Ser. No. 61/151,291 filed Feb. 10, 2009 and U.S. provisional application Ser. No. 61/173,755 filed Apr. 29, 2009, each of which are incorporated by reference herein in their entireties.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof. In one embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

In another embodiment, the invention provides a method of treating moderate to severe hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/dl, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/dl, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

In one embodiment, the subject or subject group being treated in accordance with methods of the invention has previously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline;
(b) reduced Apo B levels compared to baseline;
(c) increased HDL-C levels compared to baseline;
(d) no increase in LDL-C levels compared to baseline;
(e) a reduction in LDL-C levels compared to baseline;
(f) a reduction in non-HDL-C levels compared to baseline;
(g) a reduction in vLDL levels compared to baseline;
(h) an increase in apo A-I levels compared to baseline;
(i) an increase in apo A-I/apo B ratio compared to baseline;
(j) a reduction in lipoprotein A levels compared to baseline;
(k) a reduction in LDL particle number compared to baseline;
(l) an increase in LDL size compared to baseline;
(m) a reduction in remnant-like particle cholesterol compared to baseline;
(n) a reduction in oxidized LDL compared to baseline;
(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;
(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;
(q) a reduction in homeostasis model insulin resistance compared to baseline;
(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;
(s) a reduction in intracellular adhesion molecule-1 compared to baseline;
(t) a reduction in interleukin-6 compared to baseline;
(u) a reduction in plasminogen activator inhibitor-1 compared to baseline;
(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;
(w) an increase in serum or plasma EPA compared to baseline;
(x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or
(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n−3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no or no increase in RBC DHA.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking an additional measurement of said one or more markers.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about

1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a)-(y) described immediately above.

In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least

about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 26 or more of outcomes (a)-(y) described immediately above.

Parameters (a)-(y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo A1, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6^{th} Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (e.g. greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000

mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In another embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with meth-

ods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage form is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage faun comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a

plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In another embodiment, the invention provides use of any composition described herein for treating moderate to severe hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder.

EXAMPLES

A multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≧500 mg/dL. The primary objective of the study is to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≧500 mg/dL and ≧1500 mg/dL (≧5.65 mmol/L and ≧16.94 mmol/L).

The secondary objectives of this study are the following:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid and apolipoprotein profiles;
3. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
4. To determine the effect of AMR101 on oxidized LDL;
5. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
6. To determine the effect of AMR101 on insulin resistance;
7. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
8. To determine the effects of AMR101 2 g daily and 4 g daily on the incorporation of fatty acids into red blood cell membranes and into plasma phospholipids;
9. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
10. To explore the relationship between an increase in red blood cell membrane eicosapentaenoic acid (EPA) concentrations and the reduction in fasting TG levels.

The population for this study is men and women (women of childbearing potential will need to be on contraception or practice abstinence) >18 years of age with a body mass index ≧45 kg/m^2 who are not on lipid-altering therapy or are currently on lipid-altering therapy. Patients currently on statin therapy (with or without ezetimibe) will be evaluated by the investigator as to whether this therapy can be safely discontinued at screening, or if it should be continued. If statin therapy (with or without ezetimibe) is to be continued, dose(s) must be stable for weeks prior to randomization. Patients taking non-statin, lipid-altering medications (niacin >200 mg/day, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), must be able to safely discontinue non-statin, lipid-altering therapy at screening.

Approximately 240 patients will be randomized at approximately 50 centers in North America, South America, Central America, Europe, India, and South Africa. The study will be a 58- to 60-week, Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, double-blind, randomized, placebo-controlled treatment period; and (3) A 40-week, open-label, extension period.

During the screening period and double-blind treatment period, all visits are to be within ±3 days of the scheduled time. During the open-label extension period, all visits are to be within ±7 days of the scheduled time. The screening period includes a 4- or 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. s) must be stable for ≧4 weeks prior to randomization.

The screening visit (Visit 1) will occur for all patients at either 6 weeks (for patients not on lipid-altering therapy at screening or for patients who will not need to discontinue their current lipid-altering therapy) or 8 weeks (for patients who will require washout of their current lipid-altering therapy at screening) before randomization, as follows:

Patients who do not require a washout: The screening visit will occur at Visit 1 (Week −6). Eligible patients will enter a 4-week diet and lifestyle stabilization period. At the screening visit, all patients will receive counseling regarding the importance of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet. Patients who will require a washout: The screening visit will occur at Visit 1 (Week −8). Eligible patients will begin a 6-week washout period at the screening visit. Patients will receive counseling regarding the NCEP TLC diet and will receive instructions on how to follow this diet. Site personnel will contact patients who do not qualify for participation based on screening laboratory test results to instruct them to resume their prior lipid-altering medications.

At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients will enter the 2-week TG qualifying period and will have their fasting TG level measured at Visit 2 (Week −2) and Visit 3 (Week −1). Eligible patients must have an average fasting TG level ≧500 mg/dl and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L) to enter the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit 2 (Week −2) and Visit 3 (Week −1) values. If a patient's average TG level from Visit 2 and Visit 3 falls outside the required range for entry into the study, an additional sample for fasting TG measurement can be collected 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study will be based on the average (arithmetic mean) of the values from Visit 3 and Visit 3.1.

After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients will be randomly assigned to 1 of the following treatment groups:

AMR101 2 g daily,
AMR101 4 g daily, or
Placebo.

During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-I/apo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, pahnitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week −1] or if it occurs, Visit 3.1).measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide ≧90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p<0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

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.

2. The method of claim **1** wherein the subject has a fasting baseline LDL-C from about 50 mg/dl to about 300 mg/dl.

3. The method of claim **1**, wherein the subject has one or more of: a baseline fasting non-HDL-C of about 200 mg/dl to about 400 mg/dl, a baseline fasting total cholesterol of about 250 mg/dl to about 400 mg/dl, a baseline fasting VLDL-C of

about 140 mg/dl to about 200 mg/dl, and/or a baseline fasting HDL-C of about 10 mg/dl to about 60 mg/dl.

4. The method of claim **1**, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject.

5. The method of claim **1**, wherein said administering effects a reduction in apolipoprotein B in the subject.

6. The method of claim **1**, wherein said administering effects a reduction in VLDL-C in the subject.

7. The method of claim **1**, wherein said administration effects reduction in fasting triglycerides of at least about 20% without increasing LDL-C in the subject.

8. The method of claim **1**, wherein each capsule comprises about 950 mg of ethyl eicosapentaenoate.

9. The method of claim **1**, wherein each capsule comprises about 975 mg of ethyl eicosapentaenoate.

10. The method of claim **1**, wherein each capsule comprises about 1 g of ethyl eicosapentaenoate.

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.

12. The method of claim **11** wherein the subject has a fasting baseline LDL-C from about 50 mg/dl to about 300 mg/dl.

13. The method of claim **11**, wherein the subject has one or more of: a baseline fasting non-HDL-C of about 200 mg/dl to about 400 mg/dl, a baseline fasting total cholesterol of about 250 mg/dl to about 400 mg/dl, a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, and/or a baseline fasting HDL-C of about 10 mg/dl to about 60 mg/dl.

14. The method of claim **11**, wherein said administering effects a reduction in fasting triglycerides of at least about 10% without increasing LDL-C by more than 5% in the subject compared to placebo control.

15. The method of claim **11**, wherein said administering effects a reduction in apolipoprotein B in the subject compared to placebo control.

16. The method of claim **11**, wherein said administering effects a reduction in VLDL-C in the subject compared to placebo control.

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.

18. The method of claim **11**, wherein each capsule comprises about 950 mg of ethyl eicosapentaenoate.

19. The method of claim **11**, wherein each capsule comprises about 975 mg of ethyl eicosapentaenoate.

20. The method of claim **11**, wherein each capsule comprises about 1 g of ethyl eicosapentaenoate.

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(12) **United States Patent**
Manku et al.

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(54) **METHODS OF TREATING HYPERTRIGLYCERIDEMIA**

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USPC **514/183**; 514/549; 424/451

(58) **Field of Classification Search**
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See application file for complete search history.

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(57) **ABSTRACT**

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related disease and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof.

9 Claims, No Drawings

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METHODS OF TREATING HYPERTRIGLYCERIDEMIA

This application is a continuation of co-pending U.S. application Ser. No. 13/711,329 filed Dec. 11, 2012, which is a continuation of U.S. application Ser. No. 13/623,450, filed on Sep. 20, 2012, which is a continuation of U.S. application Ser. No. 13/349,153 filed on Jan. 12, 2012, which is a continuation of U.S. application Ser. No. 12/702,889 filed on Feb. 9, 2010 which claims priority to U.S. provisional application Ser. No. 61/151,291 filed Feb. 10, 2009 and U.S. provisional application Ser. No. 61/173,755 filed Apr. 29, 2009, each of which are incorporated by reference herein in their entireties.

BACKGROUND

Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dislipidemia, congestive heart failure and stroke. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

In various embodiments, the present invention provides methods of treating and/or preventing cardiovascular-related diseases and, in particular, a method of blood lipid therapy comprising administering to a subject in need thereof a pharmaceutical composition comprising eicosapentaenoic acid or a derivative thereof. In one embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid (or derivative thereof).

In one embodiment, a pharmaceutical composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell. In another embodiment, the composition contains substantially no or no amount of docosahexaenoic acid (DHA) or derivative thereof such as ethyl-DHA (DHA-E).

In another embodiment, the invention provides a method of treating moderate to severe hypethiglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

While the present invention is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present invention.

In one embodiment, the invention provides a method for treatment and/or prevention of a cardiovascular-related disease. The term "cardiovascular-related disease" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

In one embodiment, the present invention provides a method of blood lipid therapy comprising administering to a subject or subject group in need thereof a pharmaceutical composition as described herein. In another embodiment, the subject or subject group has hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia and/or very high triglycerides.

In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of at least about 300 mg/dl, at least about 400 mg/dl, at least about 500 mg/dl, at least about 600 mg/dl, at least about 700 mg/dl, at least about 800 mg/di, at least about 900 mg/dl, at least about 1000 mg/dl, at least about 1100 mg/dl, at least about 1200 mg/dl, at least about 1300 mg/dl, at least about 1400 mg/di, or at least about 1500 mg/dl, for example about 400 mg/dl to about 2500 mg/dl, about 450 mg/dl to about 2000 mg/dl or about 500 mg/dl to about 1500 mg/dl.

In one embodiment, the subject or subject group being treated in accordance with methods of the invention has previously been treated with Lovaza® and has experienced an increase in, or no decrease in, LDL-C levels and/or non-HDL-C levels. In one such embodiment, Lovaza® therapy is discontinued and replaced by a method of the present invention.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of free EPA (or mean thereof in the case of a subject group) not greater than about 0.70 nmol/ml, not greater than about 0.65 nmol/ml, not greater than about 0.60 nmol/ml, not greater than about 0.55 nmol/ml, not greater than about 0.50 nmol/ml, not greater than about 0.45 nmol/ml, or not greater than about 0.40 nmol/ml. In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a baseline fasting plasma level (or mean thereof) of free EPA, expressed as a percentage of total free fatty acid, of not more than about 3%, not more than about 2.5%, not more than about 2%, not more than about 1.5%, not more than about 1%, not more than about 0.75%, not more than about 0.5%, not more than about 0.25%, not more than about 0.2% or not more than about 0.15%. In one such embodiment, free plasma EPA and/or total fatty acid levels are determined prior to initiating therapy.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline absolute plasma level of total fatty acid (or mean thereof) not greater than about 250 nmol/ml, not greater than about 200 nmol/ml, not greater than about 150 nmol/ml, not greater than about 100 nmol/ml, or not greater than about 50 nmol/ml.

In another embodiment, the subject or subject group being treated in accordance with methods of the invention exhibits a fasting baseline plasma, serum or red blood cell membrane EPA level not greater than about 70 μg/ml, not greater than about 60 μg/ml, not greater than about 50 μg/ml, not greater than about 40 μg/ml, not greater than about 30 μg/ml, or not greater than about 25 μg/ml.

In another embodiment, methods of the present invention comprise a step of measuring the subject's (or subject group's mean) baseline lipid profile prior to initiating therapy. In another embodiment, methods of the invention comprise the step of identifying a subject or subject group having one or more of the following: baseline non-HDL-C value of about 200 mg/dl to about 400 mg/dl, for example at least about 210 mg/dl, at least about 220 mg/dl, at least about 230 mg/dl, at least about 240 mg/dl, at least about 250 mg/dl, at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl, at least about 290 mg/dl, or at least about 300 mg/dl; baseline total cholesterol value of about 250 mg/dl to about 400 mg/dl, for example at least about 260 mg/dl, at least about 270 mg/dl, at least about 280 mg/dl or at least about 290 mg/dl; baseline vLDL-C value of about 140 mg/dl to about 200 mg/dl, for example at least about 150 mg/dl, at least about 160 mg/dl, at least about 170 mg/dl, at least about 180 mg/dl or at least about 190 mg/dl; baseline HDL-C value of about 10 to about 60 mg/dl, for example not more than about 40 mg/dl, not more than about 35 mg/dl, not more than about 30 mg/dl, not more than about 25 mg/dl, not more than about 20 mg/dl, or not more than about 15 mg/dl; and/or baseline LDL-C value of about 50 to about 300 mg/dl, for example not less than about 100 mg/dl, not less than about 90 mg/dl, not less than about 80 mg/dl, not less than about 70 mg/dl, not less than about 60 mg/dl or not less than about 50 mg/dl.

In a related embodiment, upon treatment in accordance with the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits one or more of the following outcomes:

(a) reduced triglyceride levels compared to baseline;
(b) reduced Apo B levels compared to baseline;
(c) increased HDL-C levels compared to baseline;
(d) no increase in LDL-C levels compared to baseline;
(e) a reduction in LDL-C levels compared to baseline;
(f) a reduction in non-HDL-C levels compared to baseline;
(g) a reduction in vLDL levels compared to baseline;
(h) an increase in apo A-I levels compared to baseline;
(i) an increase in apo A-I/apo B ratio compared to baseline;
(j) a reduction in lipoprotein A levels compared to baseline;
(k) a reduction in LDL particle number compared to baseline;
(l) an increase in LDL size compared to baseline;
(m) a reduction in remnant-like particle cholesterol compared to baseline;
(n) a reduction in oxidized LDL compared to baseline;
(o) no change or a reduction in fasting plasma glucose (FPG) compared to baseline;
(p) a reduction in hemoglobin A_{1c} (HbA_{1c}) compared to baseline;
(q) a reduction in homeostasis model insulin resistance compared to baseline;
(r) a reduction in lipoprotein associated phospholipase A2 compared to baseline;
(s) a reduction in intracellular adhesion molecule-1 compared to baseline;
(t) a reduction in interleukin-6 compared to baseline;
(u) a reduction in plasminogen activator inhibitor-1 compared to baseline;
(v) a reduction in high sensitivity C-reactive protein (hsCRP) compared to baseline;
(w) an increase in serum or plasma EPA compared to baseline;
(x) an increase in red blood cell (RBC) membrane EPA compared to baseline; and/or
(y) a reduction or increase in one or more of serum phospholipid and/or red blood cell content of docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA), palmitic acid (PA), staeridonic acid (SA) or oleic acid (OA) compared to baseline.

In one embodiment, upon administering a composition of the invention to a subject, the subject exhibits a decrease in triglyceride levels, an increase in the concentrations of EPA and DPA (n-3) in red blood cells, and an increase of the ratio of EPA:arachidonic acid in red blood cells. In a related embodiment the subject exhibits substantially no or no increase in RBC DHA.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking an additional measurement of said one or more markers.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about

1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more, any 24 or more, or all 25 of outcomes (a)-(y) described immediately above.

In another embodiment, upon treatment with a composition of the present invention, the subject or subject group exhibits one or more of the following outcomes:

(a) a reduction in triglyceride level of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(c) substantially no change in HDL-C levels, no change in HDL-C levels, or an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(d) a less than 60% increase, a less than 50% increase, a less than 40% increase, a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(e) a decrease in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) as compared to baseline;

(f) a reduction in vLDL levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(g) an increase in apo A-I levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(h) an increase in apo A-I/apo B ratio of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(i) a reduction in lipoprotein (a) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(j) a reduction in mean LDL particle number of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(k) an increase in mean LDL particle size of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(l) a reduction in remnant-like particle cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(m) a reduction in oxidized LDL of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(n) substantially no change, no significant change, or a reduction (e.g. in the case of a diabetic subject) in fasting plasma glucose (FPG) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(o) substantially no change, no significant change or a reduction in hemoglobin A_{1c} (HbA_{1c}) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% (actual % change or median % change) compared to baseline;

(p) a reduction in homeostasis model index insulin resistance of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(q) a reduction in lipoprotein associated phospholipase A2 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at

least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(r) a reduction in intracellular adhesion molecule-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(s) a reduction in interleukin-6 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(t) a reduction in plasminogen activator inhibitor-1 of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(u) a reduction in high sensitivity C-reactive protein (hsCRP) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% (actual % change or median % change) compared to baseline;

(v) an increase in serum, plasma and/or RBC EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 100%, at least about 200% or at least about 400% (actual % change or median % change) compared to baseline;

(w) an increase in serum phospholipid and/or red blood cell membrane EPA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, r at least about 50%, at least about 100%, at least about 200%, or at least about 400% (actual % change or median % change) compared to baseline;

(x) a reduction or increase in one or more of serum phospholipid and/or red blood cell DHA, DPA, AA, PA and/or OA of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline; and/or

(y) a reduction in total cholesterol of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% (actual % change or median % change) compared to baseline.

In one embodiment, methods of the present invention comprise measuring baseline levels of one or more markers set forth in (a)-(y) prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a)-(y) are determined, and subsequently taking a second measurement of the one or more markers as measured at baseline for comparison thereto.

In another embodiment, upon treatment with a composition of the present invention, for example over a period of about 1 to about 200 weeks, about 1 to about 100 weeks, about 1 to about 80 weeks, about 1 to about 50 weeks, about 1 to about 40 weeks, about 1 to about 20 weeks, about 1 to about 15 weeks, about 1 to about 12 weeks, about 1 to about 10 weeks, about 1 to about 5 weeks, about 1 to about 2 weeks or about 1 week, the subject or subject group exhibits any 2 or more of, any 3 or more of, any 4 or more of, any 5 or more of, any 6 or more of, any 7 or more of, any 8 or more of, any 9 or more of, any 10 or more of, any 11 or more of, any 12 or more of, any 13 or more of, any 14 or more of, any 15 or more of, any 16 or more of, any 17 or more of, any 18 or more of, any 19 or more of, any 20 or more of, any 21 or more of, any 22 or more of, any 23 or more of, any 24 or more of, or all 26 or more of outcomes (a)-(y) described immediately above.

Parameters (a)-(y) can be measured in accordance with any clinically acceptable methodology. For example, triglycerides, total cholesterol, HDL-C and fasting blood sugar can be sample from serum and analyzed using standard photometry techniques. VLDL-TG, LDL-C and VLDL-C can be calculated or determined using serum lipoprotein fractionation by preparative ultracentrifugation and subsequent quantitative analysis by refractometry or by analytic ultracentrifugal methodology. Apo Al, Apo B and hsCRP can be determined from serum using standard nephelometry techniques. Lipoprotein (a) can be determined from serum using standard turbidimetric immunoassay techniques. LDL particle number and particle size can be determined using nuclear magnetic resonance (NMR) spectrometry. Remnants lipoproteins and LDL-phospholipase A2 can be determined from EDTA plasma or serum and serum, respectively, using enzymatic immunoseparation techniques. Oxidized LDL, intercellular adhesion molecule-1 and interleukin-6 levels can be determined from serum using standard enzyme immunoassay techniques. These techniques are described in detail in standard textbooks, for example Tietz Fundamentals of Clinical Chemistry, 6^{th} Ed. (Burtis, Ashwood and Borter Eds.), WB Saunders Company.

In one embodiment, subjects fast for up to 12 hours prior to blood sample collection, for example about 10 hours.

In another embodiment, the present invention provides a method of treating or preventing primary hypercholesterolemia and/or mixed dyslipidemia (Fredrickson Types IIa and IIb) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein. In a related embodiment, the present invention provides a method of reducing triglyceride levels in a subject or subjects when treatment with a statin or niacin extended-release monotherapy is considered inadequate (Frederickson type IV hyperlipidemia).

In another embodiment, the present invention provides a method of treating or preventing risk of recurrent nonfatal myocardial infarction in a patient with a history of myocardial infarction, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of slowing progression of or promoting regression of atherosclerotic disease in a patient in need thereof, comprising administering to a subject in need thereof one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating or preventing very high serum triglyceride levels (e.g. Types IV and V hyperlipidemia) in a patient in need thereof, comprising administering to the patient one or more compositions as disclosed herein.

In another embodiment, the present invention provides a method of treating subjects having very high serum triglyceride levels (e.g. greater than 1000 mg/dl or greater than 2000 mg/dl) and that are at risk of developing pancreatitis, comprising administering to the patient one or more compositions as disclosed herein.

In one embodiment, a composition of the invention is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the invention include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

In one embodiment, a composition for use in methods of the invention comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid. In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1-C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester. In another embodiment, the EPA comprises In one embodiment, the EPA comprises all-cis eicosa-5,8,11,14,17-pentaenoic acid ethyl ester.

In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

In another embodiment, EPA is present in a composition useful in accordance with methods of the invention in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg or about 2500 mg.

In another embodiment, a composition useful in accordance with the invention contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present invention.

In one embodiment, a composition of the invention comprises ultra-pure EPA. The term "ultra-pure" as used herein with respect to EPA refers to a composition comprising at least 95% by weight EPA (as the term "EPA" is defined and exemplified herein). Ultra-pure EPA comprises at least 96% by weight EPA, at least 97% by weight EPA, or at least 98% by weight EPA, wherein the EPA is any form of EPA as set forth herein.

In another embodiment, a composition useful in accordance with methods of the invention contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the invention contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

In another embodiment, a composition useful in accordance with the invention has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20° C.) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20° C.) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

In another embodiment, a composition useful in accordance with the invention comprises, consists of or consists essentially of at least 95% by weight ethyl eicosapentaenoate (EPA-E), about 0.2% to about 0.5% by weight ethyl octadecatetraenoate (ODTA-E), about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate (NDPA-E), about 0.2% to about 0.45% by weight ethyl arachidonate (AA-E), about 0.3% to about 0.5% by weight ethyl eicosatetraenoate (ETA-E), and about 0.05% to about 0.32% ethyl heneicosapentaenoate (HPA-E). In another embodiment, the composition is present in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 95%, 96% or 97%, by weight, ethyl eicosapentaenoate, about 0.2% to about 0.5% by weight ethyl octadecatetraenoate, about 0.05% to about 0.25% by weight ethyl nonaecapentaenoate, about 0.2% to about 0.45% by weight ethyl arachidonate, about 0.3% to about 0.5% by weight ethyl eicosatetraenoate, and about 0.05% to about 0.32% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, about 500 mg to about 1 g of the composition is provided in a capsule shell.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96% by weight ethyl eicosapentaenoate, about 0.22% to about 0.4% by weight ethyl octadecatetraenoate, about 0.075% to about 0.20% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.40% by weight ethyl arachidonate, about 0.3% to about 0.4% by weight ethyl eicosatetraenoate and about 0.075% to about 0.25% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell. In one embodiment, the dosage faun is a gel or liquid capsule and is packaged in blister packages of about 1 to about 20 capsules per sheet.

In another embodiment, compositions useful in accordance with the invention comprise, consist essential of, or consist of at least 96%, 97% or 98%, by weight, ethyl eicosapentaenoate, about 0.25% to about 0.38% by weight ethyl octadecatetraenoate, about 0.10% to about 0.15% by weight ethyl nonaecapentaenoate, about 0.25% to about 0.35% by weight ethyl arachidonate, about 0.31% to about 0.38% by weight ethyl eicosatetraenoate, and about 0.08% to about 0.20% ethyl heneicosapentaenoate. Optionally, the composition contains not more than about 0.06%, about 0.05%, or about 0.04%, by weight, DHA or derivative there of such as ethyl-DHA. In one embodiment the composition contains substantially no or no amount of DHA or derivative there of such as ethyl-DHA. The composition further optionally comprises one or more antioxidants (e.g. tocopherol) or other impurities in an amount of not more than about 0.5% or not more than 0.05%. In another embodiment, the composition comprises about 0.05% to about 0.4%, for example about 0.2% by weight tocopherol. In another embodiment, the invention provides a dosage form comprising about 500 mg to about 1 g of the foregoing composition in a capsule shell.

In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

In one embodiment, a subject being treated in accordance with methods of the invention is not otherwise on lipid-altering therapy, for example statin, fibrate, niacin and/or ezetimibe therapy.

In another embodiment, compositions useful in accordance with methods of the invention are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not

the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

A composition for use in accordance with the invention can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

In another embodiment, the invention provides use of any composition described herein for treating moderate to severe hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 500 mg/dl to about 1500 mg/dl and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

In one embodiment, compositions of the invention, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5-10° C.) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

In one embodiment, the invention provides use of a composition as described herein in manufacture of a medicament for treatment of any of a cardiovascular-related disease. In another embodiment, the subject is diabetic.

In one embodiment, a composition as set forth herein is packaged together with instructions for using the composition to treat a cardiovascular disorder.

EXAMPLES

A multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≧500 mg/dL. The primary objective of the study is to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with fasting TG levels ≧500 mg/dl and ≦1500 mg/dL (≧5.65 mmol/L and ≦16.94 mmol/L).

The secondary objectives of this study are the following:

1. To determine the safety and tolerability of AMR101 2 g daily and 4 g daily;
2. To determine the effect of AMR101 on lipid and apolipoprotein profiles;
3. To determine the effect of AMR101 on low-density lipoprotein (LDL) particle number and size;
4. To determine the effect of AMR101 on oxidized LDL;
5. To determine the effect of AMR101 on fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c});
6. To determine the effect of AMR101 on insulin resistance;
7. To determine the effect of AMR101 on high-sensitivity C-reactive protein (hsCRP);
8. To determine the effects of AMR101 2 g daily and 4 g daily on the incorporation of fatty acids into red blood cell membranes and into plasma phospholipids;
9. To explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
10. To explore the relationship between an increase in red blood cell membrane eicosapentaenoic acid (EPA) concentrations and the reduction in fasting TG levels.

The population for this study is men and women (women of childbearing potential will need to be on contraception or practice abstinence) >18 years of age with a body mass index ≦45 kg/m^2 who are not on lipid-altering therapy or are currently on lipid-altering therapy. Patients currently on statin therapy (with or without ezetimibe) will be evaluated by the investigator as to whether this therapy can be safely discontinued at screening, or if it should be continued. If statin therapy (with or without ezetimibe) is to be continued, dose(s) must be stable for ≧4 weeks prior to randomization. Patients taking non-statin, lipid-altering medications (niacin >200 mg/day, fibrates, fish oil, other products containing omega-3 fatty acids, or other herbal products or dietary supplements with potential lipid-altering effects), either alone or in combination with statin therapy (with or without ezetimibe), must be able to safely discontinue non-statin, lipid-altering therapy at screening.

Approximately 240 patients will be randomized at approximately 50 centers in North America, South America, Central America, Europe, India, and South Africa. The study will be a 58- to 60-week, Phase 3, multi-center study consisting of 3 study periods: (1) A 6- to 8-week screening period that includes a diet and lifestyle stabilization and washout period and a TG qualifying period; (2) A 12-week, double-blind, randomized, placebo-controlled treatment period; and (3) A 40-week, open-label, extension period.

During the screening period and double-blind treatment period, all visits are to be within ±3 days of the scheduled time. During the open-label extension period, all visits are to be within ±7 days of the scheduled time. The screening period includes a 4- or 6-week diet and lifestyle stabilization period and washout period followed by a 2-week TG qualifying period. s) must be stable for weeks prior to randomization.

The screening visit (Visit 1) will occur for all patients at either 6 weeks (for patients not on lipid-altering therapy at screening or for patients who will not need to discontinue their current lipid-altering therapy) or 8 weeks (for patients who will require washout of their current lipid-altering therapy at screening) before randomization, as follows:

Patients who do not require a washout: The screening visit will occur at Visit 1 (Week—6). Eligible patients will enter a 4-week diet and lifestyle stabilization period. At the screening visit, all patients will receive counseling regarding the importance of the National Cholesterol Education Program (NCEP) Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet. Patients who will require a washout: The screening visit will occur at Visit 1 (Week—8). Eligible patients will begin a 6-week washout period at the screening visit. Patients will receive counseling regarding the NCEP TLC diet and will receive instructions on how to follow this diet. Site personnel will contact patients who do not qualify for participation based on screening laboratory test results to instruct them to resume their prior lipid-altering medications.

At the end of the 4-week diet and lifestyle stabilization period or the 6-week diet and stabilization and washout period, eligible patients will enter the 2-week TG qualifying period and will have their fasting TG level measured at Visit 2 (Week—2) and Visit 3 (Week—1). Eligible patients must have an average fasting TG level ≧500 mg/dl and ≦1500 mg/dL mmol/L and (≧5.65 mmol/L and ≦16.94 mmol/L) to enter the 12-week double-blind treatment period. The TG level for qualification will be based on the average (arithmetic mean) of the Visit 2 (Week—2) and Visit 3 (Week—1) values.

If a patient's average TG level from Visit 2 and Visit 3 falls outside the required range for entry into the study, an additional sample for fasting TG measurement can be collected 1 week later at Visit 3.1. If a third sample is collected at Visit 3.1, entry into the study will be based on the average (arithmetic mean) of the values from Visit 3 and Visit 3.1.

After confirmation of qualifying fasting TG values, eligible patients will enter a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients will be randomly assigned to 1 of the following treatment groups:

AMR101 2 g daily,

AMR101 4 g daily, or

Placebo.

During the double-blind treatment period, patients will return to the site at Visit 5 (Week 4), Visit 6 (Week 11), and Visit 7 (Week 12) for efficacy and safety evaluations.

Patients who complete the 12-week double-blind treatment period will be eligible to enter a 40-week, open-label, extension period at Visit 7 (Week 12). All patients will receive open-label AMR101 4 g daily. From Visit 8 (Week 16) until the end of the study, changes to the lipid-altering regimen are permitted (e.g., initiating or raising the dose of statin or adding non-statin, lipid-altering medications to the regimen), as guided by standard practice and prescribing information. After Visit 8 (Week 16), patients will return to the site every 12 weeks until the last visit at Visit 11 (Week 52).

Eligible patients will be randomly assigned at Visit 4 (Week 0) to receive orally AMR101 2 g daily, AMR101 4 g daily, or placebo for the 12-week double-blind treatment period. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 g of AMR101. During the double-blind treatment period, patients will take 2 capsules (AMR101 or matching placebo) in the morning and 2 in the evening for a total of 4 capsules per day. Patients in the AMR101 2 g/day treatment group will receive 1 AMR101 1 g capsule and 1 matching placebo capsule in the morning and in the evening. Patients in the AMR101 4 g/day treatment group will receive 2 AMR101 1 g capsules in the morning and evening.

Patients in the placebo group will receive 2 matching placebo capsules in the morning and evening. During the extension period, patients will receive open-label AMR101 4 g daily. Patients will take 2 AMR101 1 g capsules in the morning and 2 in the evening.

The primary efficacy variable for the double-blind treatment period is percent change in TG from baseline to Week 12 endpoint. The secondary efficacy variables for the double-blind treatment period include the following:

- Percent changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), calculated low-density lipoprotein cholesterol (LDL-C), calculated non-high-density lipoprotein cholesterol (non-HDL-C), and very low-density lipoprotein cholesterol (VLDL-C) from baseline to Week 12 endpoint;
- Percent change in very low-density lipoprotein TG from baseline to Week 12;
- Percent changes in apolipoprotein A-I (apo A-I), apolipoprotein B (apo B), and apo A-I/apo B ratio from baseline to Week 12;
- Percent changes in lipoprotein(a) from baseline to Week 12 (selected sites only);
- Percent changes in LDL particle number and size, measured by nuclear magnetic resonance, from baseline to Week 12 (selected sites only);
- Percent change in remnant-like particle cholesterol from baseline to Week 12 (selected sites only);
- Percent change in oxidized LDL from baseline to Week 12 (selected sites only);
- Changes in FPG and HbA_{1c} from baseline to Week 12;
- Change in insulin resistance, as assessed by the homeostasis model index insulin resistance, from baseline to Week 12;
- Percent change in lipoprotein associated phospholipase A2 from baseline to Week 12 (selected sites only);
- Change in intracellular adhesion molecule-1 from baseline to Week 12 (selected sites only);
- Change in interleukin-6 from baseline to Week 12 (selected sites only);
- Change in plasminogen activator inhibitor-1 from baseline to Week 12 (selected sites only);
- Change in hsCRP from baseline to Week 12 (selected sites only);
- Change in serum phospholipid EPA content from baseline to Week 12;
- Change in red blood cell membrane EPA content from baseline to Week 12; and
- Change in serum phospholipid and red blood cell membrane content in the following fatty acids from baseline to Week 12: docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmitic acid, stearic acid, and oleic acid.

The efficacy variable for the open-label extension period is percent change in fasting TG from extension baseline to end of treatment. Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, and physical examinations.

For TG, TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, baseline will be defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week—1] or if it occurs, Visit 3.1) measurements. Baseline for all other efficacy parameters will be the Visit 4 (Week 0) measurement.

For TC, HDL-C, calculated LDL-C, calculated non-HDL-C, and VLDL-C, Week 12 endpoint will be defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoint for all other efficacy parameters will be the Visit 7 (Week 12) measurement.

The primary efficacy analysis will be performed using a 2-way analysis of covariance (ANCOVA) model with treatment as a factor and baseline TG value as a covariate. The least-squares mean, standard error, and 2-tailed 95% confidence interval for each treatment group and for each comparison will be estimated. The same 2-way ANCOVA model will be used for the analysis of secondary efficacy variables.

The primary analysis will be repeated for the per-protocol population to confirm the robustness of the results for the intent-to-treat population.

The primary efficacy variable will be the percent change in fasting TG levels from baseline to Week 12. A sample size of 69 completed patients per treatment group will provide ≧90% power to detect a difference of 30% between AMR101 and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p < 0.01$. To accommodate a 15% drop-out rate from randomization to completion of the double-blind treatment period, a total of 240 randomized patients is planned (80 patients per treatment group).

What is claimed is:

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 of ethyl

eicosapentaenoate and not more than about 4% docosahexaenoic acid or its esters, by weight of all fatty acids.

2. The method of claim **1**, wherein the subject has a fasting baseline LDL-C from about 50 mg/dl to about 300 mg/dl.

3. The method of claim **1**, wherein the subject has one or more of: a baseline fasting non-HDL-C of about 200 mg/dl to about 300 mg/dl, a baseline fasting total cholesterol of about 250 mg/dl to about 300 mg/dl, a baseline fasting VLDL-C of about 140 mg/dl to about 200 mg/dl, or a baseline fasting HDL-C of about 10 mg/dl to about 80 mg/dl.

4. The method of claim **1**, wherein 12 weeks of said daily administration is effective to reduce triglycerides by at least about 30% without increasing LDL-C in subjects who have fasting triglycerides levels of at least 500 mg/dl.

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.

6. The method of claim **1**, wherein 12 weeks of said daily administration is effective to reduce VLDL-C in subjects who have fasting triglycerides levels of at least 500 mg/dl.

7. The method of claim **1**, wherein the subject has a fasting baseline triglyceride level of 500 mg/dl to 1500 mg/dl.

8. The method of claim **1** wherein the pharmaceutical composition is present in one or more dosage units.

9. The method of claim **8** wherein the dosage units are capsules.

* * * * *

CERTIFICATE OF SERVICE AND FILING

I hereby certify that I electronically filed the foregoing document with the Clerk of the Court of the United States Court of Appeal for the Federal Circuit by using the Court's CM/ECF filing system.

I certify that all participants in the case are registered CM/ECF users and that all counsel were served via CM/ECF on May 12, 2020.

/s/ Jonathan E. Singer
Jonathan E. Singer

CERTIFICATE OF COMPLIANCE

The undersigned attorney certifies that the opening brief for Appellants Amarin Pharma, Inc. and Amarin Pharmaceuticals Ireland Limited, complies with the type-volume limitation set forth in Fed. R. App. P. 32(a)(7)(B). The relevant portions of the brief, including all footnotes, contain 13,984 words as determined by Microsoft Word.

Dated: May 12, 2020

/s/ Jonathan E. Singer

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