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Established Name Omega-3-carboxylic acids
(Proposed) Trade Name Epanova
Therapeutic Class Lipid lowering agent
Applicant Omthera Pharmaceuticals

Formulation(s) Capsules
Dosing Regimen 2 grams or 4 grams daily
(proposed)
Indication(s) Severe hypertriglyceridemia
Intended Population(s) Patients with TG \geq 500 mg/dL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical efficacy and safety review were conducted by two different reviewers for this application. This document focuses on the clinical efficacy review; please see Dr. Giovanni Cizza's safety review for details of those analyses.

Omthera Pharmaceuticals submitted this 505(b)(1) New Drug Application (NDA) for omega-3-carboxylic acids, trade name Epanova, for the treatment of severe hypertriglyceridemia (TG \geq 500 mg/dL). Epanova is an omega-3 fatty acid preparation primarily composed of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The applicant proposes that since Epanova is a free fatty acid formulation, it is more bioavailable than previously approved fish oil products.

In support of this application, the applicant conducted one pivotal Phase 3 trial (EVOLVE) in patients with severe hypertriglyceridemia (N=399), one trial (ECLIPSE) in statin-treated patients with TG between 200 and 500 mg/dL (N=646), and also submitted supporting long term safety data from four trials with Crohn's disease patients (N=804).

Although the pivotal trial, EVOLVE, was conducted with three doses of Epanova (2g, 3g, and 4g) as compared to placebo, the applicant proposed only the 2g and the 4g doses for final approval. I agree with the applicant that the 3g dose provided results that were sometimes less effective (depending on the lipid parameter) than the 2g dose and therefore provided little benefit over the 2g dose. Therefore, approval of the 3g dose was not in consideration.

The question was whether to approve only the 2g or the 4g dose or both for approval. In fact, the 2g and 4g dose were very similar in efficacy with overlapping 95% confidence intervals. In pharmacokinetic TG dose-response curves, it was not possible to discern a difference between the 2g and the 4g dose of Epanova (or even the 3g dose). Furthermore, the pharmacodynamic study, EVOLVE, was not designed to detect treatment differences between doses of Epanova.

The following table summarizes the TG lowering effect of the four treatment arms from the EVOLVE trial.

Table 1: Changes in Triglyceride by Treatment Arm, EVOLVE study

	Olive Oil	Epanova 2g	Epanova 3g	Epanova 4g
TG % change from Baseline, LS Mean	-4.26	-25.94	-25.46	-30.86
p value		0.005	0.007	< 0.001
95% CI	(-13.07, 5.44)	(-32.84, -18.33)	(-32.44, -17.75)	(-37.32, -23.74)
Median change from Baseline (mg/dL)	-71.3	-170.7	-163.9	-178.0

The 4g dose of Epanova provided a 5% greater TG reduction (percent change from Baseline to End of Treatment) over the 2g dose of -31% vs. -26%. Compared to placebo, both the 2g and 4g dose resulted in statistically significant decreases in TG, p=0.005 and p<0.001, respectively. The median absolute TG reduction was 171 mg/dL with 2g Epanova vs 178 mg/dL with the 4g Epanova. Over the 12 week period of the pivotal EVOLVE trial, the TG response with the 4g drifted up to the vicinity of the 2g TG response while the 2g response stayed fairly constant. The non-HDL-C reduction with the 4g dose was 2% greater over the 2g dose.

In examining whether the different doses of Epanova or placebo actually moved patients' TG to <500 mg/dL at the end of the trial, there was a numerical difference between the 2g and the 4g dose. In the Epanova 2g group, 39% of patients achieved TG <500 mg/dL compared to 52% of patients in the Epanova 4g group. In the placebo group, 37% of patients achieved TG<500 mg/dL at the end of the trial. In an exploratory analysis of the Cochran-Armitage trend test for 2g, 3g, and 4g doses of Epanova, the two-sided p value was 0.08.

Table 2: Patients Who Achieved TG <500 mg/dL at End of Treatment, EVOLVE study

TG<500 mg/dL	Placebo N=98	Epanova 2 g N=95	Epanova 3 g N=94	Epanova 4 g N=95
Yes, n (%)	36 (37%)	37 (39%)	42 (45%)	49 (52%)
No, n (%)	62 (63%)	58 (61%)	52 (55%)	46 (28%)

The safety profile between the 2g and 4g Epanova was similar with 5.0% of patients on 2g Epanova and 5.1% of patients in the 4g Epanova reporting an adverse event (AE) leading to discontinuation. No patients on placebo reported an AE leading to

discontinuation. Approximately 40% of patients on 2g, 44% of patients on 4g, and 26% of patients on placebo reported any adverse event.

The applicant contends that because of the unique pharmacology of Epanova, the TG lowering dose-response between the 2 g and 4 g regimens had an apparent curvilinearity, i.e., incremental lipid lowering was not dose-proportional but dose-dependent. This curvilinear dose-response is also observed with statins, i.e. doubling the dose leads to a disproportionate incremental benefit (6% reduction). Therefore, the applicant proposes the benefit-risk with both Epanova dosages will offer a clinical option to effectively treat patients with severe hypertriglyceridemia.

I agree with the applicant that approving both the 2g and 4g doses will provide physicians the opportunity to individualize treatment options for patients with severe hypertriglyceridemia. Therefore, I recommend both the Epanova 2 g and 4 g daily doses with the instruction to individualize therapy according to patient response and tolerability.

1.2 Risk Benefit Assessment

The risk benefit assessment is favorable for approval of Epanova 2g and 4g doses. The safety review demonstrated an acceptable profile that was consistent with previously approved omega-3 fish oil products. Although there were more gastrointestinal AEs reported for 4g vs. 2g, most were considered mild or moderate in severity. Both doses reduced TG statistically significantly compared to placebo.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

2.1 Product Information

Epanova (omega-3-carboxylic acids) is a fish oil product that includes the polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). It is not less than 85% (w/w) PUFA content of which approximately 550

mg/g is EPA and approximately 200 mg/g is DHA. The sum of the EPA and DHA content is approximately 750 mg/g. The total amount of omega-3 free fatty acids is not less than 800 mg/g. The drug product is a coated reddish-brown soft gelatin 1 gram capsule.

The applicant proposes Epanova is a new molecular entity (NME) because the “role of each fatty acid in the activity of a complex natural mixture such as this should not be considered in isolation”. Therefore the applicant is seeking 5 years of exclusivity. This case has been referred to the CDER Exclusivity Board which will determine Epanova’s exclusivity status.

2.2 Tables of Currently Available Treatments for Proposed Indications

Other products currently available for the indication of severe hypertriglyceridemia are niacin, fibrates, and omega-3-acid ethyl esters.

Table 3: Currently Available Products for Severe Hypertriglyceridemia

Trade Name	NDA (date of approval)	Class of Drugs
Lopid	NDA 18,422 (21 December 1981)	Gemfibrozil
Tricor (micronized)	NDA 19,304 (31 Dec 1993)	Fenofibrate
Tricor	NDA 21,656 (5 Nov 2004)	Fenofibrate
Antara	NDA 21,695 (30 Nov 2004)	Fenofibrate
Triglide	NDA 21,350 (7 May 2005)	Fenofibrate
Lipofen	NDA 21, 612 (11 January 2006)	Fenofibrate
Fenoglide	NDA 22,118 (10 Aug 2007)	Fenofibrate
Trilipix	NDA 22,224 (15 Dec 2008)	Choline fenofibrate
Fibricor	NDA 22,418 (14 August 2009)	Fenofibric acid
Niaspan	NDA 20,381 (28 July 1997)	Niacin extended-release
Simcor	NDA 22,078 (15 February 2008)	Niacin extended-release; Simvastatin
Advicor	NDA 21,249 (17 Dec 2001)	Niacin extended-release; Lovastatin
Lovaza	NDA 21,654 (10 November 2004)	Omega-3-acid ethyl esters
Vascepa	NDA 202057 (26 July 2012)	Icosapent ethyl

2.3 Availability of Proposed Active Ingredient in the United States

In the US, there are two fish oil prescription products available for the treatment of severe hypertriglyceridemia, Lovaza and Vascepa. Lovaza (omega-3-acid ethyl esters) is a mixture that contains at least 900 mg of ethyl esters of omega-3 fatty acids, principally EPA and DHA. Vascepa (icosapent ethyl) contains only EPA as its active ingredient.

2.4 Important Safety Issues With Consideration to Related Drugs

With regard to Lovaza, which has been available since 2004, there have been four areas of potential safety concern: increases in LDL-C, liver enzymes, blood glucose, and a possible increase in bleeding risk.

The increase in LDL-C is thought to be due to the increased activity of lipoprotein lipase (LPL) activity. This increased activity enhances the conversion of very low density lipoprotein (VLDL) and intermediate-density lipoproteins (IDL) to LDL-C.¹

The current Lovaza label states that patients with hepatic impairment should have ALT and AST monitored periodically during therapy. This stems from a greater number of patients with upward shifts in ALT levels, without a concurrent increase in AST shifts in the Integrated Summary of Safety (ISS) of Lovaza monotherapy trials.

Historically, some studies have raised concern that omega-3 ethyl ester consumption could increase fasting plasma glucose (FPG) without corresponding increase in HbA1C.² However, a recent Cochrane meta-analysis suggested that neither the FPG nor the HbA1c increased with omega-3 ethyl ester therapy.³ Pooled data from the Lovaza NDA datasets (post-hoc) showed a slight increase in median FPG in the Lovaza treatment group (median change +6.5mg/dL) as compared to the placebo group (+2 mg/dL).

Metabolism of omega-3 fatty acids, specifically EPA, produces eicosanoids of the thromboxane A3 and leukotriene 5 series, which are associated with reduced platelet aggregation, increased vasodilation, and inhibited leukocyte chemotaxis.⁴ Omega-3 acid ethyl esters have been shown in vitro to significantly reduce platelet aggregation by

1 Sacks FM, Zheng C, Cohn JS. Complexities of plasma apolipoprotein C-III metabolism. *J Lipid Res.* 2011; 52 (6):1067-70.

2 Balk EM, Lichtenstein AH, Chung M, et al. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis* 2006; 189:19-30.

3 Hartweg J, Perera R, Montori VM, Dinneen SF, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. *Cochrane Database of Systematic Review.* 2008, Issue 1. Art. No.: CD003205. DOI: 10.1002/14651858.CD003205.pub2

4 Schmidt EB, Dyerberg J. Omega-3 fatty acids. Current status in cardiovascular medicine. *Drugs.* 1994; 47:405-24

reducing production of thromboxane A2 and increasing production of thromboxane A3. The relationship of these in vitro findings to bleeding risk is much less clear. Currently the labeling for Lovaza includes cautionary statements with regard to bleeding risk.

In addition to safety issues related to Lovaza, ethyl EPA has been investigated in a large study in Japan. In the “Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS)”: a randomized open-label, blinded endpoint analysis, 18,645 Japanese patients were randomly assigned to 1800 mg of EPA plus a statin or statin alone. Safety concerns in this study included changes in creatine phosphokinase (CPK) and liver enzymes. Adverse effects (AEs) that were more common in the treatment group than in the control group included gastrointestinal disturbances, skin abnormality, and hemorrhage (cerebral, fundus, epitaxis, subcutaneous). No further information on bleeding events is available from the published JELIS report.

The Agency issued a review of the safety of EPA and DHA administered or consumed together in the Federal Register of June 5, 1997 (US FDA Substances Affirmed as Generally Recognized as Safe, 1997). This review focused on potentially adverse effects of these omega-3 fatty acids on bleeding time, control of blood sugar in type 2 diabetics, and LDL-C concentrations. The review was undertaken as part of the Agency’s assessment of the safety of menhaden oil as a direct human food ingredient. Menhaden are the primary source of fishmeal, used as food for poultry and pen-raised fish, such as salmon. Menhaden oil is known to have the highest concentrations of EPA (13.1%) and DHA (6.7%).

With respect to effects on bleeding time, the FDA concluded that although EPA and DHA appeared to cause small, dose-related increases in bleeding time of unclear clinical relevance, bleeding time increases associated with the use of 3g/day or less of EPA plus DHA either do not occur or are of no adverse significance.

With respect to the effects on glycemic control in type 2 diabetics, the FDA concluded that a dose-related effect is likely, and may be clinically relevant at high daily intake levels, but a daily intake of 3g/day or less of EPA and DHA causes no clinically significant effects on glycemic control.

With respect to effects of EPA and DHA on LDL-C, the FDA concluded that there appeared to be a trend toward increased LDL-C with increased fish oil consumption in all population subgroups, with a magnitude of the increase appearing greater in populations with abnormal blood lipid levels, hypertension, diabetes, and cardiovascular disease.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

On July 30, 2002, IND (b) (4) was submitted to the Division of Gastroenterology Products for an indication in Crohn's disease.

On March 25, 2010, the applicant submitted IND 107,616 to the Division of Metabolism and Endocrinology Products (DMEP) for an indication in patients with severe hypertriglyceridemia.

On June 2, 2010 an End-of-Phase 2 meeting was held between the applicant and DMEP.

On July 2, 2010 the applicant submitted a special protocol assessment (SPA) for Study OM-EPA-003.

On August 27, 2010, a SPA No Agreement letter for Study OM-EPA-003 was issued to the applicant.

On September 30, 2010 a second SPA No Agreement letter for Study OM-EPA-003 was issued to the company.

On October 22, 2010, a SPA Agreement letter was issued to the company.

On December 17, 2010, the applicant submitted a SPA request for Study OM-EPA-004.

On January 21, 2011, the applicant submitted a special carcinogenicity protocol assessment for a 26 week transgenic mouse study #1.

On January 27, 2011, DMEP issued a SPA no agreement letter for Study OM-EPA-004.

On February 23, 2011, a SPA agreement letter was issued for the 26 week transgenic mouse study #1.

On April 8, 2011, DMEP issued an advice letter regarding termination of the flawed 26 week transgenic mouse study #1.

On May 31, 2011, DMEP issued a SPA agreement letter for Study OM-EPA-004.

On June 22, 2011, ECAC issued an agreement for 26-week transgenic mouse study #2.

On August 31, 2011, the applicant requested a SPA for Study "A Phase III, Double-Blind, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patient with Hypertriglyceridemia (STRENGTH; OM-EPA-005).

Between October 6, 2011 and January 24, 2012 there were four letters between the applicant and DMEP concerning the 26-week transgenic mouse carcinogenicity study #2.

On March 16, 2012 SPA agreement letter was issued for Study OM-EPA-005.

Between May 1, 2012 and September 12, 2012 there were four advice letters between the applicant and DMEP regarding the rat carcinogenicity study.

On September 18, 2012, the applicant submitted a Pre-NDA CMC briefing document.

On October 3, 2012, a QTc alternative agreement was reached between the agency and the applicant.

On November 14, 2012, a Pre-NDA meeting was held between DMEP and the applicant.

On December 18, 2012, DMEP issued Pre-NDA meeting minutes.

On February 15, 2013, the applicant requested NME designation for Epanova.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general, the NDA submission quality and integrity were satisfactory. The submission was well organized and information was relatively easy to find.

3.2 Compliance with Good Clinical Practices

All nonclinical studies submitted in this NDA were conducted under GLP conditions. All clinical studies submitted in this NDA were conducted under Good Clinical Practices (GCP) conditions. Statements to this effect were included in each of the study reports. As certified in the submission, no debarred investigators participated in the clinical trials.

3.3 Financial Disclosures

A signed FDA form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was included in the submission declaring the absence of financial interests and arrangements between the applicant and clinical investigators. The form was appended with a list of investigators who participated in all the Phase 2 and Phase 3 studies. See the Appendix for the Clinical Investigator Financial Disclosure Review Form.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

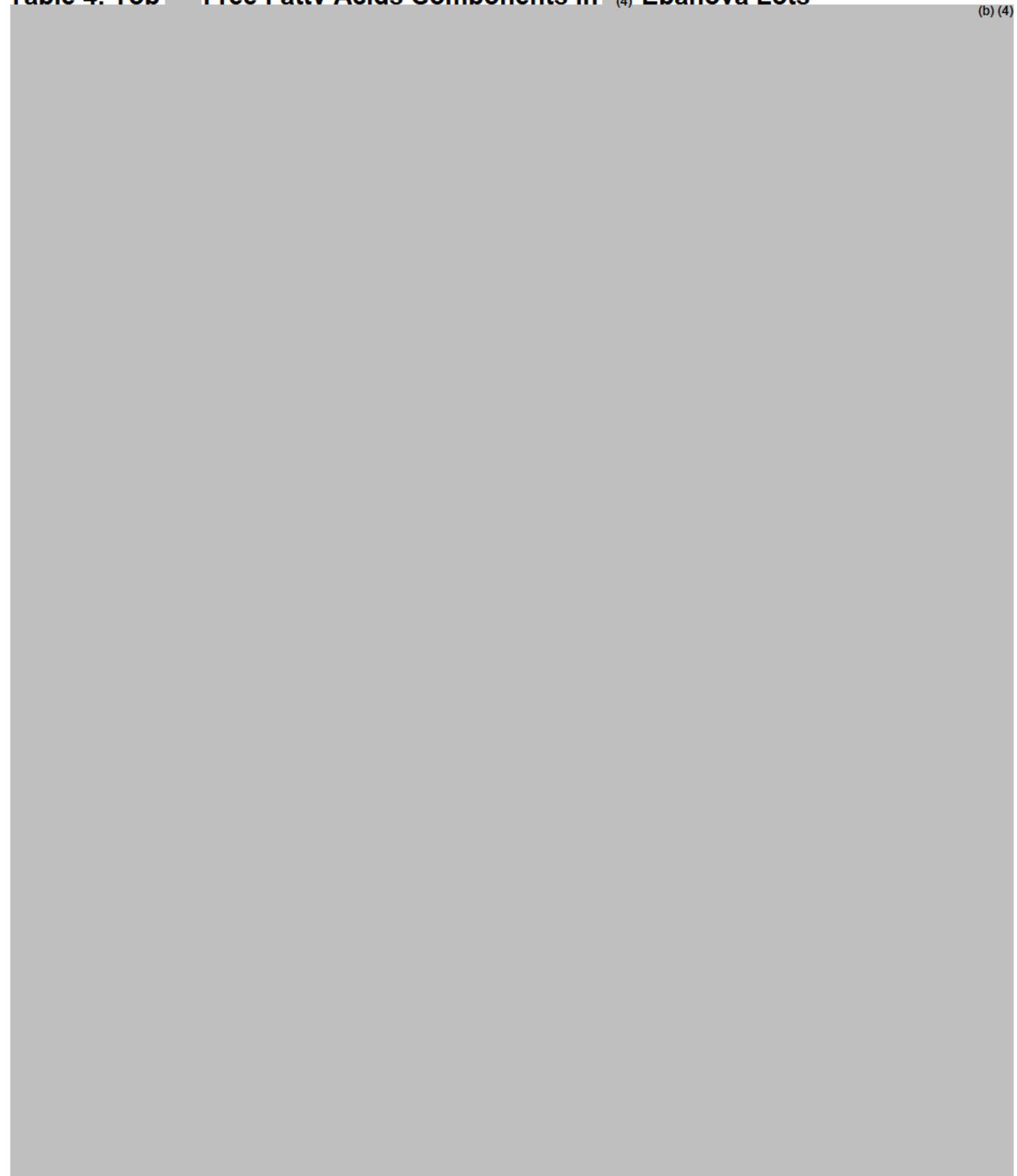
Martin Haber, Ph.D. reviewed the Chemistry, Manufacturing and Controls (CMC) data. Please see his report for a complete CMC evaluation.

The international non-proprietary name for Epanova is omega-3-carboxylic acids. The following is an excerpt from the applicant's submission.

The drug substance for Epanova is a mixture of polyunsaturated free fatty acids (PUFAs) derived from fish oils. Epanova contains not less than 85% (w/w) PUFA content of which approximately 550 mg/g is EPA, approximately 200 mg/g is DHA. The sum of the EPA and DHA content is approximately 750 mg/g. The total amount of total omega-6 free fatty acids is not more than (b) (4)%. Epanova also contains other minor components, including monounsaturated and saturated free fatty acids. It contains not more than (b) (4)% (a/a) monounsaturated and not more than (b) (4)% (a/a) saturated fatty acids. There are less than (b) (4)% (a/a) unidentified fatty acid components (b) (4)% (a/a) in Epanova.

The following table presents a relative rank ordering of the top (b) (4) fatty acid species that by area compose > 95% of the composition.

Table 4: Top ^{(b) (4)} Free Fatty Acids Components in ^{(b) (4)} Epanova Lots



(b) (4)

Source: NDA 205060 submission, Elucidation of Structure, pg. 5.

Epanova is a clear to yellow fluid oil with a slight fish-like odor and taste. It is practically insoluble in water but highly soluble in acetone, chloroform, ethanol, ethyl acetate, diethyl ether, octanol, petroleum ether (40-60) and propylene glycol.

The drug product is a soft gelatin oblong capsule containing 1,000 mg of drug substance (omega-3-carboxylic acids) and coated with a red/brown pigmented polymeric coat. The soft gelatin capsules are (b) (4) coated with poly (ethyl acrylate, methyl methacrylate), (b) (4)



Epanova capsules also contain the following inactive ingredients: 3 mg α -tocopherol (in a carrier of vegetable oil), and gelatin, glycerol, sorbitol, and purified water (components of the capsule shell).



See Dr. Mahayni's review for the biopharmaceutical perspective.

4.2 Clinical Microbiology

See Dr. Bryan Riley's review for full report. There were no microbiology deficiencies identified. The Microbial Limits specification for Epanova was acceptable from a Product Quality Microbiology perspective. Therefore, this submission was recommended for approval from the standpoint of product quality microbiology.

4.3 Preclinical Pharmacology/Toxicology

See Dr. Parvaneh Espandiari's review for the complete pharmacology/toxicology report. The pharmacology/toxicology team recommends approval of Epanova.

According to Dr. Espandiari's review, nonclinical studies were conducted in mice, rats and dogs. These studies showed the intended pharmacological effect of Epanova by decreased plasma levels of total cholesterol and triglycerides. The liver was the potential target organ toxicity across species based on increased liver enzyme activities. Increased liver enzyme activities in some studies associated with increased liver weight

and liver focal necrosis. In the 36-week dog study, 2/4 dogs at 1000mg/kg/day were noted with microscopic findings in the heart (1/4, granuloma /macrophage aggregates, epicardial, focal), and in the aorta (1/4, mineralization, adventitial focal). Safety margins to the maximum human recommended dose (MHRD) (4g/day based on a body surface area comparison) were established for 5 fold in the 4-week mouse study at 4000mg/kg/day omega-3-carboxylic acid, 2 fold in the 26- week rat study at 600 mg/kg/day omega-3-carboxylic acid, and 3 fold in the 39-week dog study at 300mg/kg/day Epanova soft gel capsules.

A full panel of genotoxicity was completed; Epanova did not exhibit genetic toxicity in the Ames assay, the chromosomal aberration study, and in the in vivo rat micronucleus study.

Two carcinogenicity studies were conducted in rats (2-year) and in Tg.rasH2 mice (26-week) oral (gavage) with omega-3-carboxylic acid. In the Tg.rasH2 mice study, no drug-related tumors up to 2000 mg/kg/day omega-3-carboxylic acid were observed (5 fold safety margin to the MHRD of 4 g/day based on a body surface area comparison).

In the rat study, benign sex cord stromal tumors of the ovaries were reported in 2000 mg/kg/day omega-3-carboxylic acid treated females (5 fold to the MHRD of 4g/day based on a body surface area comparison). This finding was statistically significant for both trend ($P=0.0005$) and pairwise comparison ($P=0.0054$). The benign ovarian sex cord tumor at 2000 mg/kg/day exceeded concurrent control and historical controls despite deviations from the protocol regarding the early discontinuation of dosing and termination for all treated animals (females were dosed for at least 65 weeks). Mortality for this study was statistically significant and cause of death was non-neoplastic based on microscopic dose-response gavage/reflux-related findings in the respiratory tract.

Findings from the reproductive and developmental toxicity studies suggested no treatment effects on reproductive performance, early embryonic development, maternal or fetal toxicity in rats up to 2000mg/kg/day (5 fold to MHRD based on a body surface area).

In pregnant rabbits, there was no effect on maternal up to 500 mg/kg/day (about 2.4 fold to MHRD of 4g/day based on a body surface area). No Observable Adverse Effect Level (NOAEL) for the embryo-fetal development was established at 100 mg/kg/day (about 0.5 fold to MHRD of 4g/day) because of skeletal malformation and ossification effects (variations) as well as visceral variations at 500 mg/kg/day. At higher exposure, 750 mg/kg/day omega-3-carboxylic acid, mortality (with evidence of abortion) and fetal skeletal variation were noted.

Late in the review cycle, CMC identified (b) (4) as a drug substance impurity in Epanova capsules and requested that Pharm/Tox assess safety. (b) (4) is an established rodent carcinogen, genotoxicant and is listed by the

International Agency for Research on Cancer (IARC) as a likely human carcinogen. Based on this a risk analysis was performed and considered along with the applicant's submitted justification for the proposed specification. The Agency informed the applicant that their specification for (b) (4) (b) (4) ppm) should be as low as possible because of the concern. The applicant indicated that (b) (4), this specification was lower than those based on ICHM7 guidelines for genotoxic impurities and that (b) (4).

4.4 Clinical Pharmacology

Mechanistic studies suggest that omega-3 fatty acid treatment lowers the TG level by both reducing the amount of hepatic TG secretion and enhancing the rate of TG clearance from circulation.^{5,6,7} Although both EPA and DHA down-regulate TG synthesis in the liver, the clinical data support the hypothesis that DHA, by regulating different hepatic transcription factors than EPA, reduces Apo C-III production, resulting in enhanced conversion of VLDL to LDL and the formation of larger, more-buoyant LDL particles as reflected by an increase in the LDL-C/Apo B ratio.⁸

4.4.2 Pharmacodynamics

The pharmacodynamics of Epanova were evaluated in the EVOLVE study, a 12-week randomized, placebo-controlled, trial in 399 patients with TG \geq 500 mg/dL and $<$ 2000mg/dL. Patients were randomized to Epanova 2g, 3g, 4g, or placebo. Study drug was administered without regard to meals. Two of the major omega-3 fatty acids in Epanova, EPA and DHA, were measured pre-treatment at Baseline (Week 0) and at End of Treatment (Week 12).

The following two figures show the pharmacodynamic relationship between the relative changes in plasma EPA and DHA and the percent TG lowering achieved by the three different doses in the EVOLVE trial.

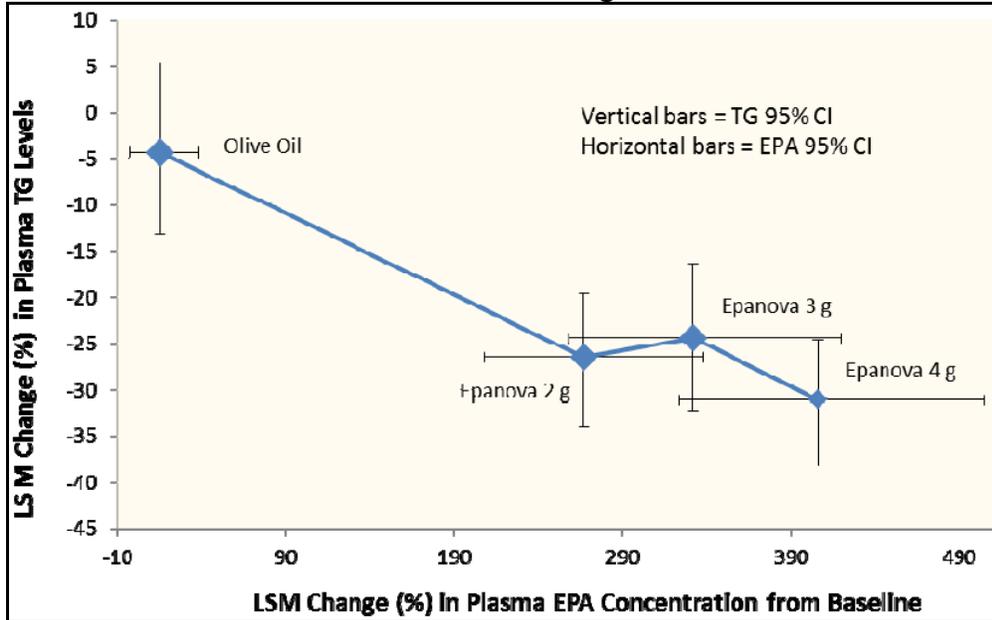
5 Khan S, Minihane AM, et al. Dietary long-chain n-3 PUFA increase LPL gene expression in adipose tissue of subjects with an atherogenic lipoprotein phenotype. *J of Lipid Res.* 2002; 43: 979-985.

6 Jump DB, Botolin D, et al. Fatty Acid Regulation of Hepatic Gene Transcription. *J Nutr.* 2005; 135:2503-2506.

7 Davidson MH. Mechanisms for the Hypotriglyceridemic Effect of Marine Omega-3 Fatty Acids. *Am J Cardiol.* 2006; 98[suppl]:27i-33i.

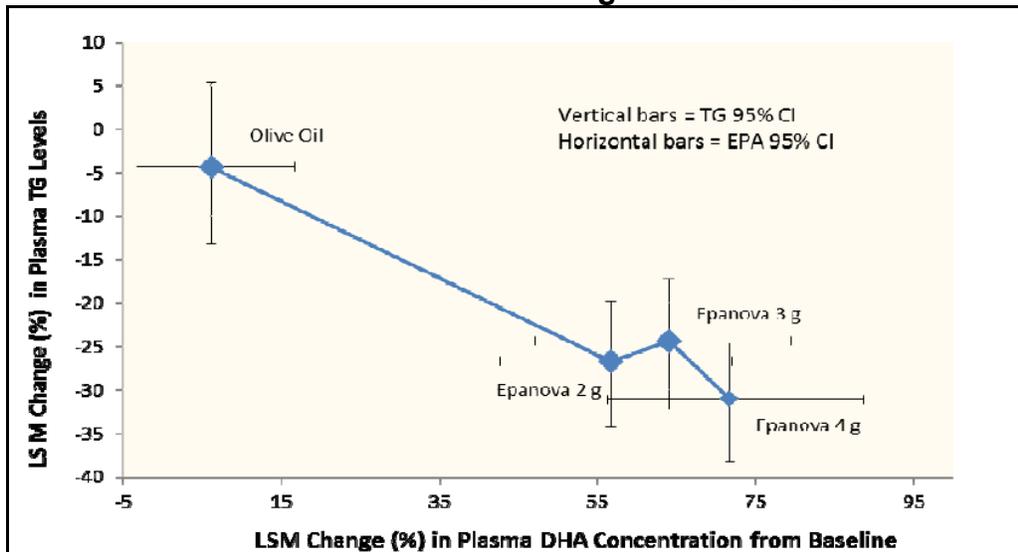
8 Chen YJ. et al. Docosahexaenoic acid suppresses the expression of FoxO and its target genes. *J Nutr Biochemistry.* 2012.

Figure 1: Pharmacodynamic Relationship between Change in Plasma EPA Concentration and Percent TG Lowering in the EVOLVE trial



Source: Summary of Clinical Pharmacology, EVOLVE trial, pg. 47.

Figure 2: Pharmacodynamic Relationship between Change in Plasma DHA Concentration and Percent TG Lowering in the EVOLVE trial



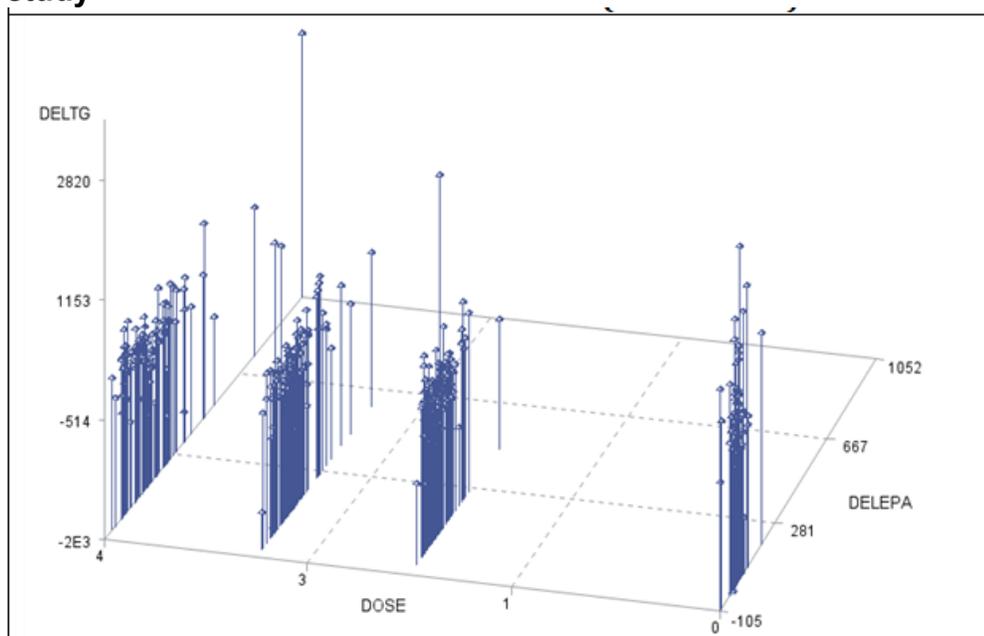
Source: Summary of Clinical Pharmacology, EVOLVE trial, pg. 47.

Administration of 2 g, 3 g and 4 g Epanova daily for 12 weeks, demonstrated dose-dependent increases in plasma EPA levels from Baseline to End of Treatment of approximately 267%, 332% and 406%, respectively, in the 2g, 3g and 4 g Epanova doses. Plasma trough DHA levels also showed a dose-response to Epanova treatment, although the increases were slighter than for EPA. Mean percent increases in plasma DHA levels were approximately 57%, 64% and 72%, respectively, for the 2 g, 3 g and 4 g/day doses.

Despite the dose-dependent increases in EPA and DHA from the 2g to the 4g dose, the TG lowering was more clustered between the two doses (point estimate of -26% to -31% with overlapping CI) suggesting there might be a plateau for TG lowering at 2g dose.

The clinical pharmacology reviewer, Dr. S. Sista plotted the change in TG vs. EPA and TG vs. DHA as a function of dose with the data from the EVOLVE study.

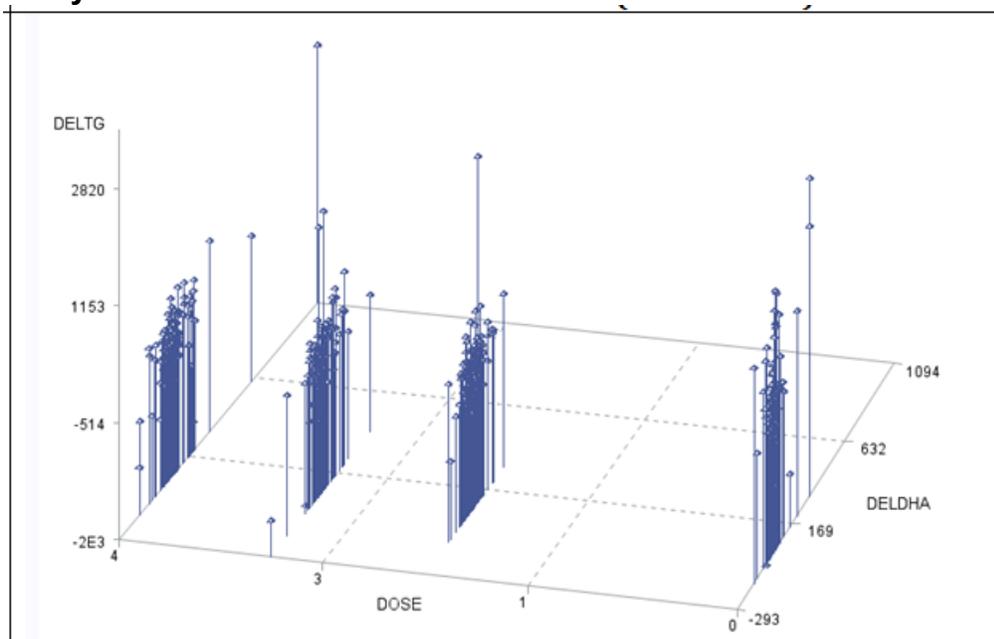
Figure 3: Plot of Change in TG vs. Change in EPA as a Function of Dose, EVOLVE study



Dose: 0 = Placebo; 2 = 2x1g; 3 =3x1g; 4= 4x1g

Source: Dr. S. Sista, clinical pharmacology reviewer

Figure 4: Plot of Change in TG vs. Change in DHA as a Function of Dose, EVOLVE study



Dose: 0 = Placebo; 2 = 2x1g; 3 = 3x1g; 4 = 4x1g

Source: Dr. S. Sista, clinical pharmacology reviewer

From these dose response curves for TG, it is difficult to distinguish a difference in TG lowering effect between the three doses of Epanova. The three different doses of Epanova elicited decreases in TG that were not distinguishable from each other, albeit each dose was statistically significantly better than placebo.

The applicant was sent a request on March 5, 2014 to expand on their justification for approving the 2g and 4g doses of Epanova as proposed in the Dosage and Administration sections of the labeling. The response from the company received March 14, 2014 is discussed in Section 6.1.8.

4.4.3 Pharmacokinetics

Bioavailability of Epanova vs. Lovaza

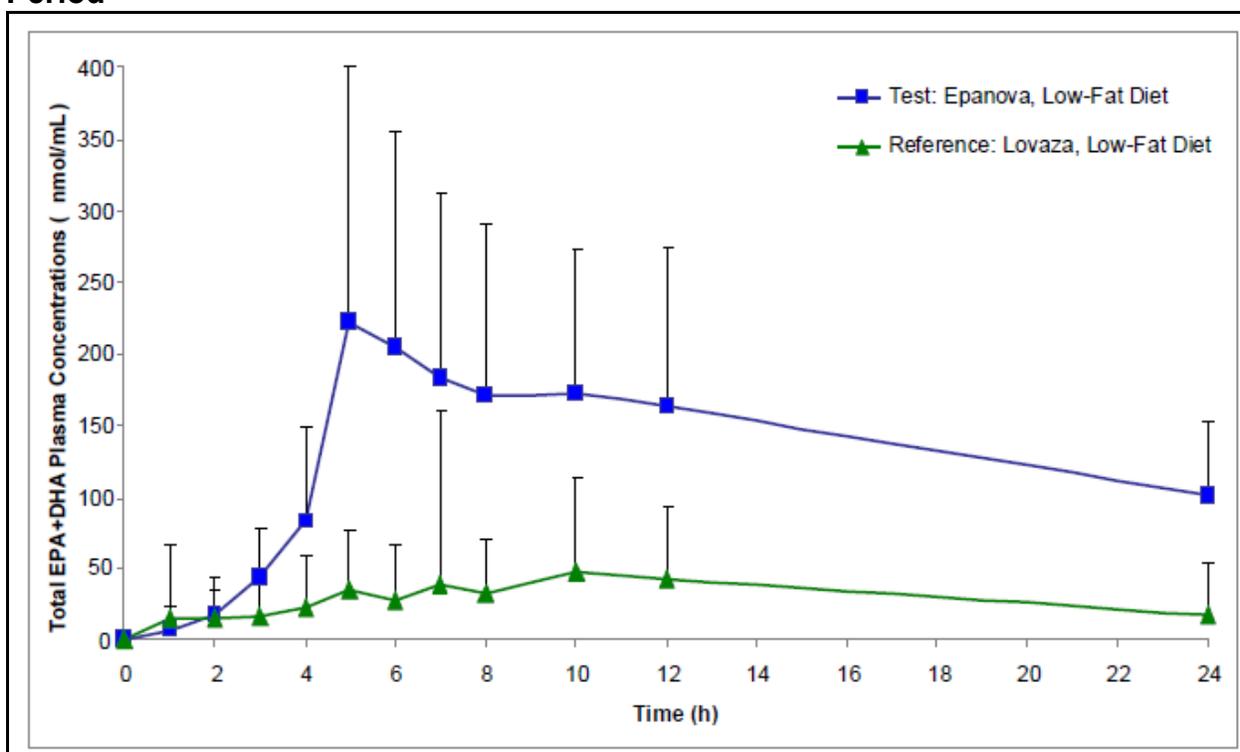
Study OM-EPA-001 was a single dose, randomized, open-label, 4-way crossover study to compare the relative bioavailability of total and free EPA and DHA from a single 4 g dose of Epanova versus Lovaza in healthy subjects (body mass index 25-35 kg/m²) after a period of fasting and a high-fat meal.

In contrast to Epanova which contains the free fatty acids of EPA and DHA, Lovaza contains omega-3-acid ethyl esters (EE) of EPA and DHA. During washout periods, subjects adhered to the low-fat Therapeutic Lifestyle Changes (TLC) diet and fast 12

hours before each clinic visit. Each 4 g dose was administered either at the end of the 12-hour fast or with a high-fat breakfast to 54 healthy adults.

According to the applicant, the mean hourly total EPA + DHA concentrations resulted in baseline-adjusted AUC_{0-t} for total EPA + DHA during the fasting period that was 4.0-fold greater with Epanova compared to Lovaza (2650.2 versus 662.0 nmol•h/mL, respectively; $p < 0.0001$). After a high-fat meal, AUC_{0-t} for Epanova was approximately 1.3-fold greater than Lovaza (4604.0 versus 3589.5 nmol•h/mL respectively; $p < 0.0001$).

Figure 5: Baseline Adjusted Mean Plasma Concentrations (SD) for Total EPA+DHA Following a Single 4g Dose of Epanova and Lovaza During Fasting Period



Source: Summary of Clin Pharmacology, Fig. 2.7.2-15, pg. 30.

According to the applicant, with a low-fat diet, the bioavailability (AUC_{0-t}) of total EPA, DHA and EPA+DHA from Epanova were significantly greater ($p < 0.0001$) relative to Lovaza approximately 9.5-fold, 2.1-fold and 4.0-fold, respectively.

With a high-fat diet, the bioavailability of total EPA and EPA+DHA from Epanova were significantly greater ($p \leq 0.0001$) relative to Lovaza (1.6-fold and 1.3-fold, respectively), however, total DHA was slightly lower (71.0% of Lovaza, $p = 0.0011$).

Table 5: Summary PK Results for Total EPA, Total DHA, and Total EPA+ DHA

Percent Ratios of LSM (Ln-Transformed Data)							
A vs. B analyses		Total EPA		Total DHA		Total EPA+DHA	
		Baseline-adjusted	Unadjusted	Baseline-adjusted	Unadjusted	Baseline-adjusted	Unadjusted
		A/B	A/B	A/B	A/B	A/B	A/B
Low-Fat EPANOV vs. Lovaza®	AUC _{0-t}	952.64	197.75	206.33	108.60	400.36	129.77
	AUC _{0-inf}	-	-	-	-	649.66	-
	C _{max}	836.15	254.60	199.59	117.71	369.66	152.50
High-Fat EPANOV vs. Lovaza®	AUC _{0-t}	161.79	134.52	70.99	95.69	128.26	110.58
	AUC _{0-inf}	119.63	-	96.17	-	108.22	-
	C _{max}	180.64	161.36	84.05	93.55	135.15	122.26
EPANOVA Low-fat vs. High-fat	AUC _{0-t}	41.90	55.60	106.40	94.30	55.90	76.90
	AUC _{0-inf}	40.80	-	61.20	-	57.00	-
	C _{max}	31.70	40.10	55.50	75.10	39.30	56.60
Lovaza® Low-fat vs. High-fat	AUC _{0-t}	7.40	38.80	37.90	83.90	18.90	66.40
	AUC _{0-inf}	1.60	-	-	-	2.80	-
	C _{max}	7.20	26.60	24.50	60.80	15.30	46.70

Note: Total comprises esterified and unesterified plasma EPA and DHA.
 Source: [OM-EPA-001 \(ECLIPSE\)](#), [Table 11.4.2](#), [Table 11.4.3](#), [Table 11.4.4](#)

Source: Summary of Clin Pharm, Table 2.7.2-7, pg. 32.

In summary, the applicant concludes that Study OM-EPA-001 confirmed that the free fatty acid (FFA) formulation of Epanova had superior bioavailability (4-fold increase in EPA absorption) over the ethyl ester (EE) formulation of Lovaza under the conditions of low-fat and high-fat feeding during single, 4 g dose administrations. The Clinical Pharmacology reviewer will make his own conclusions after his assessment of the data.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Study / Objectives of Study	Study Design and Type of Control Number of Patients	Dosage Regimen Duration, Test Products	Healthy Subjects or Diagnosis of Patients
PK/BA Study OM-EPA-001 Phase II (ECLIPSE) To compare the bioavailability of EPA and DHA, assessed by measurement of the AUC in plasma, after fasting and a high-fat	Randomized, open-label, 4-way crossover study, with 4 single-dose treatment periods and a 7-day washout in between each treatment 54 subjects enrolled	Epanova™ 4g x 2 (a.m. fasted and high fatmeal) Lovaza 4g x 2 (a.m. fasted and high-fat meal) 2 single dose of each of Epanova™ and Lovaza	Healthy M or F, age ≥ 18 years

Clinical Efficacy Review
 Iffat Nasrin Chowdhury, MD
 NDA 205060
 Epanova/omega-3-carboxylic acid

Study / Objectives of Study	Study Design and Type of Control Number of Patients	Dosage Regimen Duration, Test Products	Healthy Subjects or Diagnosis of Patients
meal, from a single 4 g dose of Epanova and Lovaza			
<p>PK/PD/BA Study OM-EPA-006 Phase I</p> <p>To determine the effect of multiple doses of Epanova™ on the pharmacokinetic and anti-coagulant activity of single dose warfarin and to compare the systemic exposure of total EPA, total DHA, and total EPA+DHA following multiple dose administration of Epanova compared to multiple-dose administration of Lovaza (omega-3 acid ethyl esters).</p>	<p>Open-label, 2- cohort, parallel design</p> <p>52 subjects enrolled</p> <p>26 enrolled in Epanova cohort</p> <p>26 enrolled in Lovaza Cohort</p>	<p>Cohort 1: Treatment A: Single dose of warfarin w/o Epanova</p> <p>Treatment B: Single dose of warfarin with 4g QD Epanova</p> <p>Cohort 2: Treatment C: 4g QD of Lovaza following low fat breakfast</p>	<p>Healthy M or F, age 18-55 years</p> <p>21 days for Cohort 1, 14 days for Cohort 2</p>
<p>PK/BA Study OM-EPA-007 Phase I</p> <p>To determine effect of multiple doses of Epanova™ on multiple-dose PK of simvastatin.</p>	<p>Open label 2- way crossover study with 2 week washout between treatments; no comparator</p> <p>52 subjects enrolled</p>	<p>Treatment A: 40mg simvastatin; 81mg of aspirin, and 4g of Epanova</p> <p>Treatment B: 40mg of simvastatin and 81mg of aspirin</p>	<p>Healthy M or F, age 18-55 years</p> <p>Treatment A: 14 days Treatment B: 14 days</p>
<p>Efficacy Study OM-EPA-003 Phase III (EVOLVE)</p> <p>To evaluate the efficacy and safety of Epanova in severe hypertriglyceridemic patients</p>	<p>Randomized, double blind, olive oil controlled, parallel group design</p> <p>12 weeks duration</p> <p>399 patients enrolled</p>	<p>Epanova 2g QD arm (n=100)</p> <p>Epanova 3g QD arm (101)</p> <p>Epanova 4g QD arm (n=99)</p> <p>Olive oil (placebo) QD arm (n=99)</p>	<p>M or F, age ≥18 years, with serum TG values at screening in the range ≥500 mg/dL and <2000 mg/dL</p>
<p>Efficacy Study OM-EPA-004</p>	<p>Randomized, double-blind, olive oil controlled, parallel</p>	<p>Epanova 2g QD</p>	<p>Patients at high risk for a future</p>

Study / Objectives of Study	Study Design and Type of Control Number of Patients	Dosage Regimen Duration, Test Products	Healthy Subjects or Diagnosis of Patients
Phase III (ESPRIT) (b) (4) in subjects with persistent hypertriglyceridemia and high-risk for cardiovascular disease.	group design 6 weeks duration 647 patients enrolled	(n=215); Epanova 4g QD (n=216) Olive oil (placebo) QD arm (n=216)	cardiovascular event (with high serum TG ≥ 200 and < 500 mg/dL despite being on a statin for at least 4 weeks prior to screening)

5.2 Review Strategy

The pivotal study for the severe hypertriglyceridemia indication is the Study OM-EPA-003 (EVOLVE) trial. I analyzed the efficacy in Section 6; the safety for EVOLVE is reviewed in Dr. Giovanni Cizza's safety report for this NDA.

The applicant also submitted Study OM-EPA-004 (ESPRIT), a trial conducted (b) (4)

(b) (4) in subjects with persistent hypertriglyceridemia (TG between 200 and 500 mg/dL). Although I describe the ESPRIT efficacy results in Section 5.3, this trial's datasets were not formally analyzed for efficacy because the study population was different from the population for the proposed indication. The safety data from this trial is included in the review by Dr. Cizza.

The clinical pharmacology team reviewed the bioavailability trial OM-EPA-001 (ECLIPSE) and the two drug-drug interaction trials OM-EPA-006 and OM-EPA-007 with warfarin and simvastatin, respectively.

5.3 Discussion of Individual Studies/Clinical Trials

Title: A 6-Week, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Add-On Epanova to Statin Therapy in Subjects with Persistent Hypertriglyceridemia and High Risk for Cardiovascular Disease (Study OM-EPA-004, or ESPRIT)

ESPRIT was a randomized, double-blind, placebo-controlled, parallel-group study in patients with hypertriglyceridemia (TG between 200 and 500 mg/dL) and high risk for cardiovascular disease who were on a maximally tolerated dose of statin. Co-

administration with Zetia® (ezetimibe) or Vytorin® (ezetimibe/simvastatin) 10/10 mg, 10/20 mg, or 10/40 mg ezetimibe/ simvastatin dosage) was allowed.

There were 6 clinic visits (3 screening/lead-in visits, 1 randomization visit, and 2 treatment visits). Patients underwent an initial 6-week washout and diet stabilization period during which they discontinued use of any non-statin lipid therapies that could be stopped, continued their current statin regimen, and followed the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.

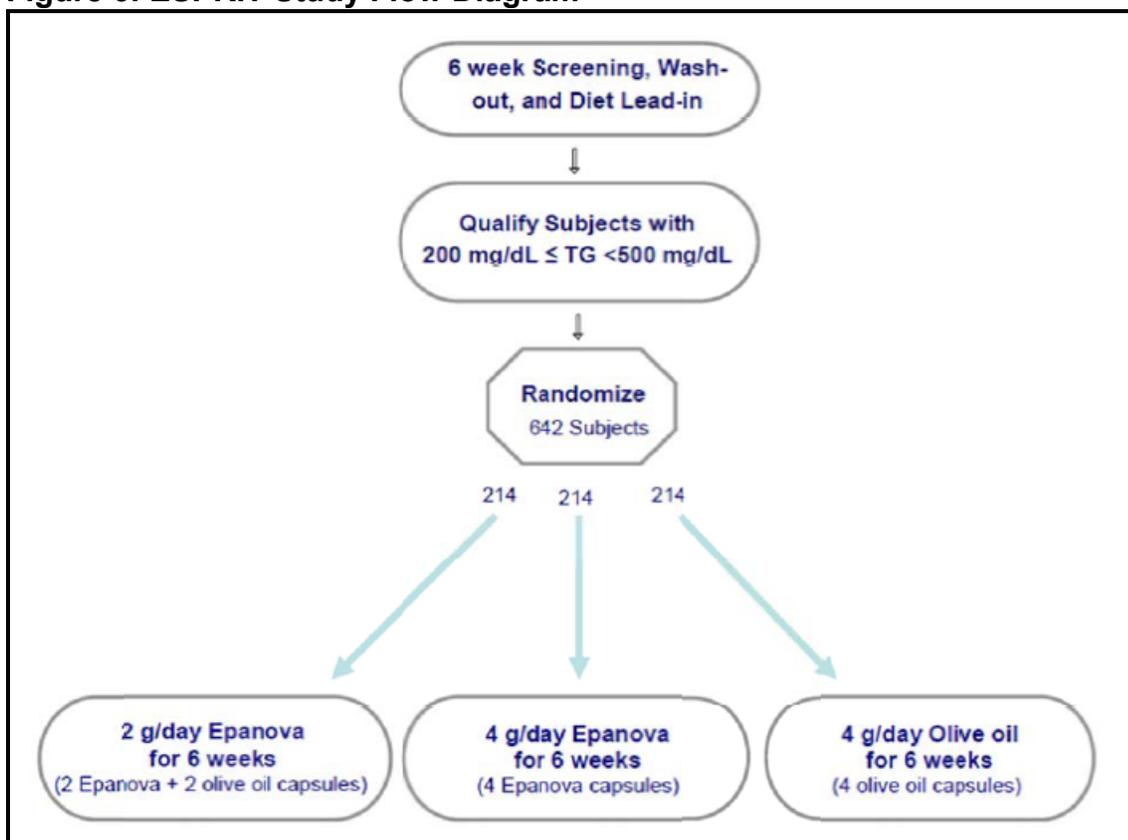
After the washout and diet stabilization period, patients with a fasting TG level ≥ 200 mg/dL and < 500 mg/dL who met all inclusion and no exclusion criteria were randomized in a 1:1:1 ratio to receive either double-blind Epanova 2 g daily, 4 g daily, or placebo (olive oil) 4 g daily for 6 weeks. Study treatment was administered as 4 capsules once daily, without regard to meals. Patients were stratified by use of statin alone or add-on use of Zetia or Vytorin, as well as by use of low-potency or high-potency statins.

The primary objective of this study was to evaluate the efficacy of adding Epanova (2 g or 4 g daily) to an optimal statin monotherapy for lowering non-HDL-C in patients with persistent hypertriglyceridemia and at high risk for cardiovascular disease.

The secondary objectives of this study were to evaluate the safety of the Epanova (2 g or 4 g daily) and statin combination therapies, and to evaluate the effects of the combination therapies on TG and other lipids and lipoproteins.

The following figure depicts the study flow diagram of the ESPRIT study.

Figure 6: ESPRIT Study Flow Diagram



Source: Study 004 report, Figure 9.1, pg. 25.

Inclusion Criteria

1. Men or women, ≥ 18 years of age.
2. Fasting TG level ≥ 200 mg/dL and < 500 mg/dL (average of Visits 2 and 3). Repeat of Visit 3 test was allowed (Visit 3a) at Investigator discretion, and the average of Visit 2 (Week -2) + Visit 3 (Week -1) + Visit 3a (repeat visit) was used as the criterion.
3. The patient was at high risk for a future cardiovascular event if at least 1 of the following criteria was present by subject history, medical records, or Investigator judgment:
 - a. Atherosclerotic cardiovascular disease as defined as a previous myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass grafting, coronary angiogram demonstrating more than a 50% stenosis, angina symptoms with a perfusion defect determined by nuclear stress testing or wall motion abnormality determined by stress echocardiogram, peripheral vascular disease (symptoms of claudication with ankle brachial index < 0.9 or angiogram showing more than 50% stenosis), carotid endarterectomy or more than

50% stenosis in a carotid artery determined by carotid ultrasound or angiogram, abdominal aortic aneurysm, or non-hemorrhagic stroke.

b. Type 2 diabetes mellitus and age ≥ 40 years.

c. High cardiovascular disease risk based on high-sensitivity C-reactive protein (hsCRP) > 2.0 mg/L (men > 50 years of age; women > 60 years of age) plus at least 1 of the following risk factors:

- Family history of premature coronary heart disease (CHD; father < 55 years, mother < 65 years),
- Low HDL-C (< 50 mg/dL, men or women),
- Hypertension or taking antihypertensive medication, or
- Cigarette smoking.

d. Impaired renal function as determined by a calculated glomerular filtration rate (GFR) < 60 mL/min/1.73m².

e. Age > 75 years.

f. Framingham or Reynolds Risk Score showing a 20% or greater 10-year risk of a coronary event utilizing TC and HDL-C values adjusted to levels prior to statin treatment (to be calculated only if none of 3a through 3e were met; see Appendices A and B of the study protocol [Appendix 16.1.1] for pre-statin lipid estimates and score calculation).

4. Was on an optimal statin dose for achieving LDL-C goals (within 110% of NCEP Adult Treatment Panel III (ATP III) for the average of Visits 2 and 3) or on a maximally tolerated statin dose (i.e., without muscle aches/weakness, liver or muscle enzyme elevations). Statin dose must have been stable for at least 4 weeks prior to screening. Co-administration with Zetia or Vytorin 10/10 mg, 10/20 mg, or 10/40 mg (ezetimibe/simvastatin dosage) was allowed.
5. Was willing to maintain current activity level and follow the TLC diet throughout the study.

Exclusion Criteria

1. Non-high-density lipoprotein cholesterol (non-HDL-C) < 90 mg/dL for the average of Visits 1 and 2. (If average was borderline, the Investigator had the option not to exclude and to measure at Visit 3; exclusion was then based on the average of Visits 1, 2, and 3).
2. Allergy or intolerance to omega-3 fatty acids and omega-3-acid ethyl esters.
3. Use of fibrates, bile acid sequestrants, or niacin or its analogues (greater than 200 mg/day) during screening.
4. Use of simvastatin 80 mg or Vytorin 10/80 mg during screening.
5. Use of any EPA or DHA products, fish oil, or medications (e.g., Lovaza) or investigational drugs (e.g., AMR101) containing EPA or DHA within 6 weeks prior to randomization.
6. Use of any supplement for the purpose of lowering plasma cholesterol during screening (e.g., red yeast rice supplements).
7. Use of weight loss drugs (including over-the-counter drugs) or programs during screening.

8. Use of erythromycin, telithromycin, clarithromycin, cyclosporine, itraconazole, ketoconazole, protease inhibitors, or nefazodone during screening.
9. Use of anticoagulants (e.g., warfarin, coumarin, heparin, Pradaxa®, or enoxaparin) during screening.
10. Use of oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/asthma) during screening.
11. Use of tamoxifen, estrogens, progestins, or testosterone that had not been stable for >4 weeks at Visit 1 and were unstable during screening.
12. Use of >750 mL/day grapefruit juice during screening.
13. Known lipoprotein lipase impairment or deficiency or apolipoprotein C-II deficiency or familial dysbetalipoproteinemia.
14. History of pancreatitis.
15. Type 1 diabetes mellitus, use of insulin, or hemoglobin A1c (HbA1c) >10% at Visit 1.
16. Poorly controlled hypertension (resting blood pressure \geq 160 mmHg systolic and/or \geq 100 mmHg diastolic) at 2 consecutive visits prior to randomization at Visit 4.
17. Uncontrolled hypothyroidism or thyroid-stimulating hormone (TSH) $>1.5 \times$ upper limit of normal (ULN) at Visit 2.
18. Recent history (within 6 months prior to Visit 1) or current significant nephrotic syndrome, pulmonary, hepatic, biliary, gastrointestinal, or immunologic disease.
19. History of cancer (except non-melanoma skin cancer or carcinoma in situ of cervix) within the previous 2 years.
20. Female subjects who were pregnant, planning to become pregnant during the study, lactating, or women of childbearing potential who were not using an acceptable method of contraception. A woman was considered of childbearing potential if she was not surgically sterile or if her last menstrual period was <12 months prior to Visit 1. Acceptable methods of contraception for this study included use of double-barrier contraception, intrauterine device or abstinence or all oral, patch, etc. hormonal or selective estrogen receptor modulator contraceptives as long as dose and type were stable for 3 months prior to screening.
21. Creatine kinase $>5.0 \times$ ULN; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>2.5 \times$ ULN at Visit 2.
22. Current or recent history (past 12 months) of drug or alcohol abuse.
23. Exposure to any investigational agent within 4 weeks prior to Visit 1.
24. Any other condition the Investigator believed would interfere with the subject's ability to provide informed consent, comply with the study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

Prohibited Medications

Use of the following was prohibited during the study at any time after Visit 1:

- Bile acid sequestrants, fibrates, or niacin or its analogues (greater than 200 mg/day).
- Simvastatin 80 mg or Vytorin 10/80 mg.
- EPA or DHA products, fish oil, or medications (e.g., Lovaza) or investigational drugs (e.g., AMR101) containing EPA or DHA.
- Any supplement for the purpose of lowering plasma cholesterol (e.g., red rice yeast supplements).
- Weight loss drugs (including over-the-counter drugs).
- Erythromycin, telithromycin, clarithromycin, cyclosporine, itraconazole, ketoconazole, protease inhibitors, or nefazodone.
- Anticoagulants (e.g., warfarin, coumarin, heparin, Pradaxa, or enoxaparin).
- Oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/ asthma).
- Grapefruit juice >750 mL/day.
- Insulin.

Permitted Medications

Lipid-altering drug regimens must have been stable for at least 4 weeks prior to Visit 1. A onetime statin adjustment was permitted at Investigator discretion within 7 days following Visit 1 in the following circumstances (following the adjustment, the statin dose must have remained stable for the remainder of study participation):

- Subjects on simvastatin 80 mg or Vytorin 10/80 mg at Visit 1 must have switched to a lower dose of simvastatin or an alternative statin in order to continue in the study.
- Subjects who were not on an adequate dose of statin to achieve LDL-C values within 110% of NCEP ATP III goal may have had their statin dose changed after Visit 1. Subjects who altered their statin therapy after Visit 1 were to delay subsequent lead-in study visits (Visits 2 and 3) to allow for approximately 4 weeks between statin therapy change and Visit 2.

Stable use (defined as no change in treatment or dosage during the 4 weeks prior to Visit 1) of medications for hypertension, type 2 diabetes mellitus (HbA1c \leq 10%), or thyroid disease (TSH \leq 1.5 \times ULN) was allowed.

Analysis Populations

The Intent-to-Treat (ITT) Population comprised all patients who were randomized. In the event that randomized subjects terminated before treatment or had no post-treatment efficacy assessments, a modified ITT Population was used.

The modified ITT Population included all subjects who received at least 1 dose of investigational product and had at least 1 valid post-randomization efficacy assessment.

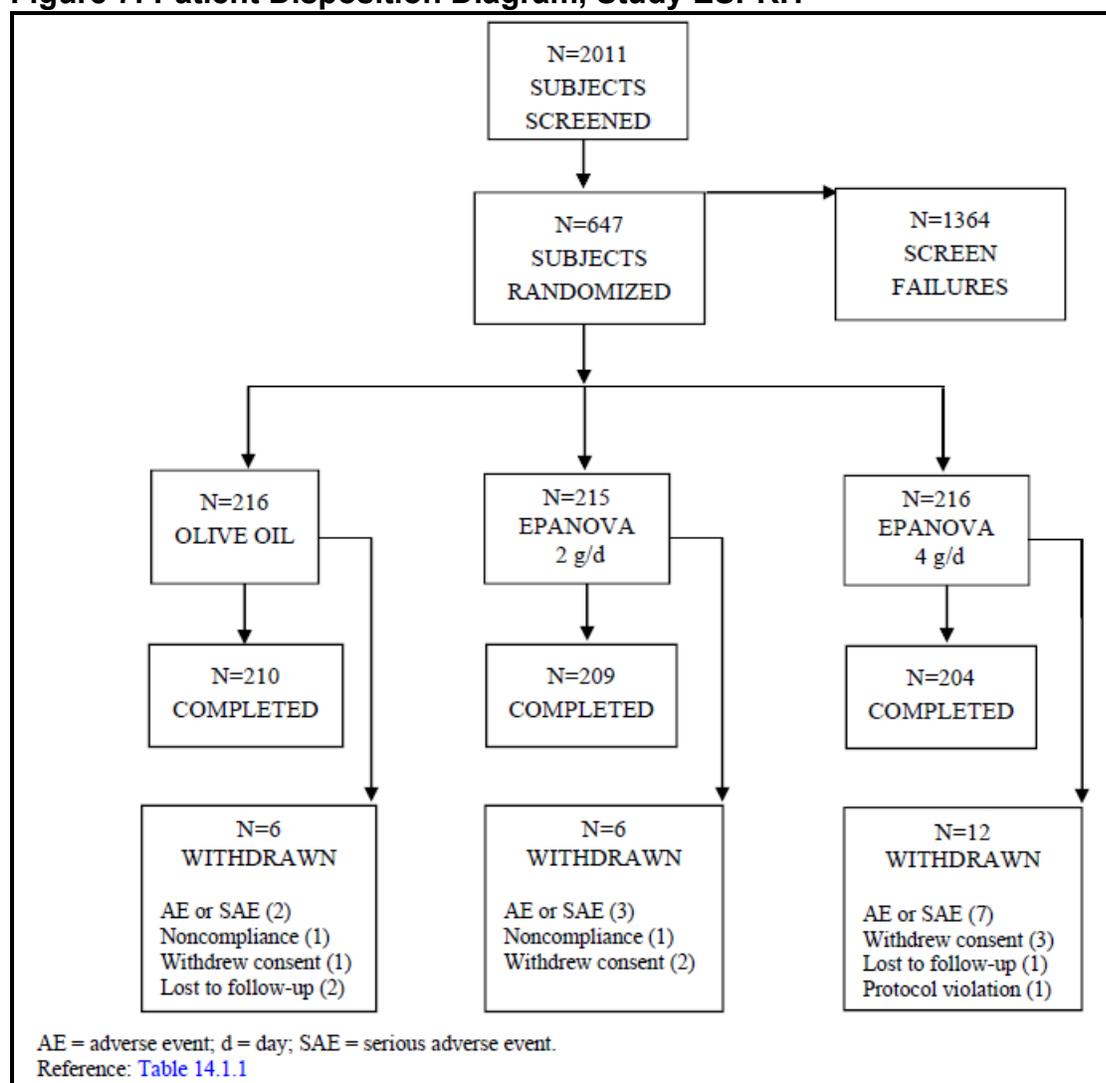
Primary and Secondary Efficacy Analysis

For each efficacy variable, value, change from baseline, and percent change from baseline (when applicable) were summarized by treatment group with descriptive statistics (n, mean, SD, median, minimum, and maximum) at each scheduled visit and also for baseline and end of treatment.

Disposition

The following diagram shows patient disposition for the ESPRIT study:

Figure 7: Patient Disposition Diagram, Study ESPRIT



Source: Study report 004, pg. 46.

There were 1364 screen failures and 647 patients randomized. The randomized patients were assigned in a 1:1:1 ratio to study treatment.

In total, 623 (96.3%) patients completed the study: 210 (97.2%) patients in the placebo group, 209 (97.2%) patients in the Epanova 2 g group, and 204 (94.4%) patients in the Epanova 4 g group.

Approximately 5.6% of patients withdrew from the 4g Epanova arm as compared to 2.8% in the 2 g Epanova arm and 2.8% in the placebo arm. The most common reason for withdrawal was due to adverse events (see table below).

Table 6: Summary Table of Patient Disposition, Study ESPRIT

	Olive Oil n (%)	Epanova 2 g n (%)	Epanova 4 g n (%)	Total n (%)
Randomized	N=216 (100.0)	N=215 (100.0)	N=216 (100.0)	N=647 (100.0)
Completed	210 (97.2)	209 (97.2)	204 (94.4)	623 (96.3)
Withdrew after randomization	6 (2.8)	6 (2.8)	12 (5.6)	24 (3.7)
Adverse event	2 (0.9)	3 (1.4)	7 (3.2)	12 (1.9)
Subject withdrew consent	1 (0.5)	2 (0.9)	3 (1.4)	6 (0.9)
Subject lost to follow-up	2 (0.9)	0 (0.0)	1 (0.5)	3 (0.5)
Noncompliance	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.3)
Protocol violation	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)

% = 100 × n/N

Source: Study Report 004, table 10.1.1, pg. 47.

Demographics

The following table summarizes the baseline characteristics of the study population. Approximately 59% of the study population was male, 94% Caucasian, with a mean age of 60.8 years.

Most of the study population was on a baseline statin monotherapy (95%) with 4.7% on a statin/ezetimibe combination. The applicant further categorized the statin users as 44% on high potency statin and 56% on low potency statin.

According to the applicant, approximately 20% of the study population had a cardiovascular disease risk estimate of greater than 20% and 30% of the population had a cardiovascular risk estimate of 10-20%.

Table 7: Demographics and Baseline Characteristics, Study ESPRIT, Safety Population

Characteristic Statistic	Olive Oil (N=215) n (%)	Epanova 2 g (N=215) n (%)	Epanova 4 g (N=216) n (%)	Total (N=646) n (%)
Age (years)				
N ^a	215	215	216	646
Mean (SD)	61.5 (9.64)	60.9 (9.95)	60.1 (9.23)	60.8 (9.61)
Age group				
N ^a	215	215	216	646
<65 years	124 (57.7)	138 (64.2)	141 (65.3)	403 (62.4)
≥65 years	91 (42.3)	77 (35.8)	75 (34.7)	243 (37.6)
Gender, n (%)				
Male	122 (56.7)	123 (57.2)	137 (63.4)	382 (59.1)
Female	93 (43.3)	92 (42.8)	79 (36.6)	264 (40.9)
Race, n (%)				
White/Caucasian	197 (91.6)	207 (96.3)	204 (94.4)	608 (94.1)
Black/African or African American	10 (4.7)	7 (3.3)	5 (2.3)	22 (3.4)
Asian	3 (1.4)	0 (0.0)	4 (1.9)	7 (1.1)
Multiple	2 (0.9)	0 (0.0)	1 (0.5)	3 (0.5)
American Indian or Alaska Native	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.3)
Native Hawaiian or Pacific Islander	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.2)
Other	1 (0.5)	1 (0.5)	1 (0.5)	3 (0.5)
Ethnicity, n (%)				
Not Hispanic or Latino	176 (81.9)	180 (84.1)	177 (81.9)	533 (82.6)
Hispanic or Latino	39 (18.1)	34 (15.9)	39 (18.1)	112 (17.4)
Statin use, n (%)				
Statin alone	205 (95.8)	206 (95.8)	204 (94.4)	615 (95.3)
Statin/Vytorin/Zetia	9 (4.2)	9 (4.2)	12 (5.6)	30 (4.7)
Statin potency, n (%)				
Low potency	121 (56.5)	121 (56.3)	119 (55.1)	361 (56.0)
High potency	93 (43.5)	94 (43.7)	97 (44.9)	284 (44.0)

^a% = 100 × n/N^a. N^a = the number of subjects with non-missing values.
 SD = standard deviation.
 Reference: [Table 14.1.4](#)

Source: Study report 004, Table 11.2.1, pg. 49

Analysis of Efficacy Endpoints

The following table shows the results of the primary and some of the secondary efficacy endpoints for Study ESPRIT.

Table 8: Percent Change in non-HDL-C, TG, and VLDL-C from Baseline to End of Treatment, ITT Population, Study ESPRIT

Statistic	Placebo N=211	Epanova 2 g N=209	Epanova 4 g N=207
Non-HDL-C mg/dL			
Baseline			
Mean (SD)	135.4 (27.80)	139.8 (26.72)	139.1 (26.73)
Median	131.7	139.0	134.7
End of Treatment			
Mean (SD)	136.4 (33.18)	136.3 (32.19)	131.6 (32.36)
Median	133.5	133.0	128.5
Percent Change from Baseline to End of Treatment			
LS mean difference relative to placebo		-2.95	-6.00
Adjusted p-value		0.0373	<0.0001
TG mg/dL			
Baseline			
Mean (SD)	279.8 (70.71)	283.7 (76.74)	287.2 (82.76)
Median	269.0	265.0	265.3
End of Treatment			
Mean (SD)	267.5 (92.74)	243.6 (88.50)	233.0 (105.79)
Median	260.0	221.5	214.5
Percent Change from Baseline to End of Treatment			
LS mean difference relative to placebo		-8.75	-14.71
Adjusted p-value		<0.0001	<0.0001
VLDL-C mg/dL			
Baseline			
Mean (SD)	45.7 (18.75)	46.9 (19.51)	47.2 (20.69)
Median	43.0	42.0	43.0
End of Treatment			
Mean (SD)	43.6 (17.85)	39.8 (15.86)	37.5 (18.85)
Median	40.8	37.0	33.0
Percent Change from Baseline to End of Treatment			
LS mean difference relative to placebo		-8.46	-15.61
p-value		0.0082	<0.0001

Source: Study Report 004, Table 11.4.1, 11.4.2, 11.4.4.

Table 9: Percent Change in LDL-C, HDL-C and TC from Baseline to End of Treatment, ITT Population, Study ESPRIT

Statistic	Placebo N=211	Epanova 2 g N=209	Epanova 4 g N=207
LDL-C mg/dL			
Baseline			
Mean (SD)	91.7 (27.28)	92.3 (26.00)	93.6 (27.64)
Median	87.0	92.0	91.0
End of Treatment			
Mean (SD)	92.8 (28.08)	96.6 (27.10)	94.2 (27.09)
Median	90.5	94.5	91.5
Percent Change from Baseline to End of Treatment			
LS mean difference relative to placebo		3.50	0.21
p-value		0.0247	0.6470
HDL-C mg/dL			
Baseline			
Mean (SD)	38.8 (8.98)	38.7 (9.87)	38.8 (10.86)
Median	37.7	37.7	36.7
End of Treatment			
Mean (SD)	39.8 (9.60)	39.8 (10.01)	40.3 (12.14)
Median	38.0	38.5	37.5
Percent Change from Baseline to End of Treatment			
LS mean difference relative to placebo		0.42	1.09
p-value		0.9881	0.9881
TC			
Baseline			
Mean (SD)	174.2 (29.45)	178.5 (29.13)	177.9 (29.07)
Median	174.0	177.0	170.3
End of Treatment			
Mean (SD)	176.2 (34.92)	176.1 (34.05)	171.9 (33.19)
Median	173.5	174.0	166.5
Percent Change from Baseline to End of Treatment			
LS mean difference relative to placebo		-2.20	-4.28
p-value		0.0489	<0.0001

Source: Study Report 004, Table 11.4.3, 11.4.5, 11.4.6.

For the primary endpoint, non-HDL-C, the least square (LS) mean difference relative to placebo in percent change from Baseline to End of Treatment was -2.95% (p-value, 0.0373) for 2 g Epanova. For 4 g Epanova the LS mean difference relative to placebo in percent change from Baseline to End of Treatment was -6.00% (p-value, <0.0001).

The LS mean differences relative to placebo in percent change from Baseline to End of Treatment for TG was -8.75% (p-value, <0.0001) for 2g Epanova and -14.71% (p-value, <0.0001) for 4g Epanova.

The LS mean differences relative to placebo in percent change from Baseline to End of Treatment for LDL-C was +3.5% (p-value, 0.0247) for 2g Epanova and +0.21% (p-value, 0.6470) for 4g Epanova.

The LS mean differences relative to placebo in percent change from Baseline to End of Treatment for HDL-C was +0.42% (p-value, 0.9881) for 2g Epanova and +1.09% (p-value, 0.9881) for 4g Epanova.

6 Review of Efficacy

6.1 Indication

Although the primary endpoint was TG in the pivotal trial, EVOLVE, the applicant proposes the following indication for this product:

“As an adjunct to diet to reduce TG, (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia”.

In patients with severe hypertriglyceridemia, the first priority is to prevent acute pancreatitis. In fact, one study found that 20% of a cohort of 129 patients referred to an endocrinology clinic for severe hypertriglyceridemia had experienced at least one episode of acute pancreatitis, the majority of which were considered severe.⁹ Notably, the geometric mean of the maximal TG levels identified among these 129 patients was 2770 mg/dL; of the 26 with a history of acute pancreatitis, the geometric mean of the maximal TG levels was 4470 mg/dL.

Although no outcomes trials exist to address the efficacy of TG lowering for preventing pancreatitis, guidelines recommend reducing TG to less than 500 mg/dL in patients with severe hypertriglyceridemia.

6.1.1 Methods

The pivotal trial for this application, EVOLVE (Study OM-EPA-003), was a prospective, double-blind trial that evaluated the efficacy and safety of Epanova in 399 patients with

⁹ Linares CL, et al. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas* 2008; 37(1):13-18.

severe hypertriglyceridemia, defined as serum TG values ≥ 500 and < 2000 mg/dL. The primary efficacy analysis evaluated the effects of each dose of Epanova, relative to placebo, on fasting TG levels after 12 weeks of treatment.

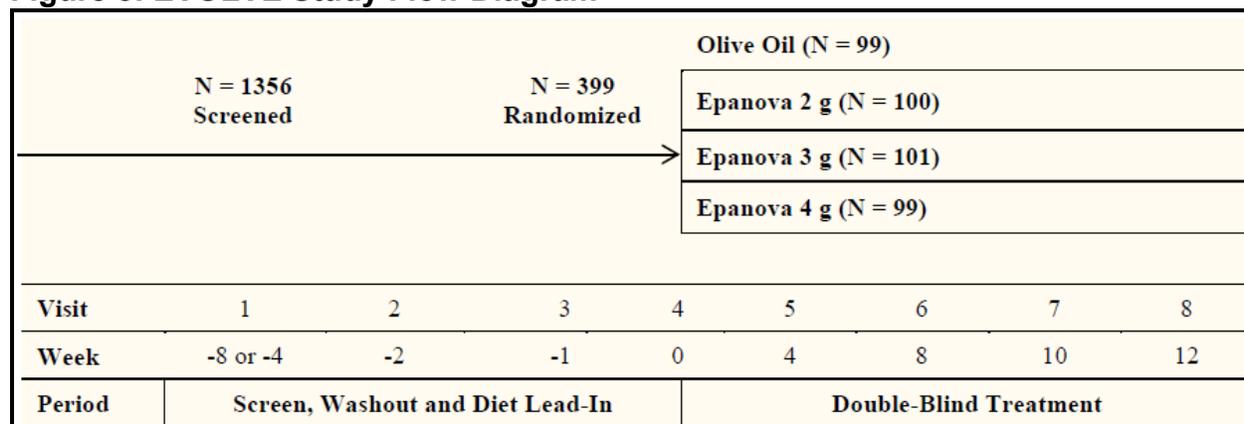
The secondary objectives were to assess the effects of each dose of Epanova on fasting levels of non-HDL-C and HDL-C.

Some of the tertiary objectives were to:

- evaluate the effects of each dose of Epanova on other lipid parameters including TC, LDL-C, TC : HDL-C ratio, and VLDL-C
- evaluate the effects of each dose of Epanova on HbA1c
- evaluate the effects of each dose of Epanova on the proportion of subjects who achieve TG < 500 mg/dL at Week 12
- evaluate the effect of each dose of Epanova on lipoprotein-associated phospholipase A2 (Lp-PLA2) and high sensitivity C-reactive protein (hs-CRP)

The following figure depicts the study flow diagram of the EVOLVE trial.

Figure 8: EVOLVE Study Flow Diagram



Source: EVOLVE Study Report, Fig. 9.1, pg. 26.

In this trial, there were eight clinic visits: one screening, two washout/diet lead-in, one randomization, and four treatment visits (see figure above).

Patients previously on omega-3 fish oil products needed to washout for 8 weeks and patients who required adjustment or addition of permitted statin, cholesterol absorption inhibitor (CAI) such as ezetimibe, or their combination needed to stabilize for 8 weeks before randomization. All other patients had a washout/diet lead-in of 4 weeks before randomization. All patients were required to follow the TLC diet.

After the washout/diet lead-in phase patients who met the entry criteria were randomized 1:1:1:1 to receive placebo (olive oil, 4 g/day), Epanova 2 g/day (plus 2

g/day placebo), Epanova 3 g/day (plus 1 g/day placebo) or Epanova 4 g/day, and continue the TLC diet.

Treatment groups had a balanced randomization of patients who were users and non-users of statins, CAI or their combinations. Patients were instructed to take their 4 capsules, at one time, every day without regard to meal timing over a 12-week treatment period.

Inclusion Criteria

1. Men or women, ≥ 18 years of age.
2. Serum TG values in the range ≥ 500 mg/dL and < 2000 mg/dL for the average of Visits 2 and 3 (Weeks -2 and -1). Repeat of Visit 3 test is allowed (Visit 3a), and the average of Visit 2 (Week -2) + Visit 3 (Week -1) + Visit 3a (repeat visit) was used as the criterion.
3. Body mass index (BMI) ≥ 20 kg/m².
4. Untreated dyslipidemia, or use of a statin or cholesterol absorption inhibitor, or their combination, if stable for 6 weeks at Visit 2 (Week -2), and prior to randomization.
5. Willing to restrict consumption of fish to no more than twice per week during the study.
6. Willingness to maintain current activity level and follow TLC diet.

Exclusion Criteria

1. Allergy or intolerance to omega-3 fatty acids, omega-3-acid ethyl esters, or fish.
2. Known lipoprotein lipase impairment or deficiency (e.g., Fredrickson Type 1) or apolipoprotein C-II deficiency or familial dysbetalipoproteinemia.
3. Unable to discontinue use of omega-3 drugs/supplements at Week -8 (Visit 1).
4. Unable to discontinue use of bile acid sequestrants, fibrates or niacin (other than niacin-containing vitamins < 200 mg), or any supplement used to alter lipid metabolism, including but not limited to: dietary fiber supplements, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols at Week -4 (Visit 1).
5. Women who are pregnant, lactating, or planning to become pregnant. Women of childbearing potential who are not using acceptable contraceptive methods. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since last menstrual period. Examples of acceptable contraceptive methods include abstinence, intrauterine device (IUD) or double barrier method. Estrogen-containing contraceptives were excluded.
6. Use of tamoxifen, estrogens or progestins that has not been stable for > 4 weeks at Visit 1, or is unstable prior to randomization.
7. Use of oral or injected corticosteroids or anabolic steroids at Visit 1 or prior to randomization.
8. History of pancreatitis.
9. History of symptomatic gallstone disease, unless treated with cholecystectomy.

10. Uncontrolled diabetes (HbA1c ≥ 9).
11. Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH) > 5 mIU/L.
12. History of cancer (other than basal cell carcinoma) in the past 2 years.
13. Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, unstable congestive heart failure requiring a change in treatment) or revascularization procedure within prior six months at Visit 1, or prior to randomization.
14. Use of anticoagulants (e.g. warfarin [Coumadin], coumarin, heparin, enoxaparin, clopidogrel).
15. Presence of an aortic aneurysm or resection of an aortic aneurysm within prior six months at Visit 1, or prior to randomization.
16. Recent history (within prior six months at Visit 1 or prior to randomization) of significant nephrotic syndrome, pulmonary, hepatic, biliary, gastrointestinal or immunologic disease.
17. Poorly controlled hypertension (resting blood pressure ≥ 160 mm Hg systolic and/or ≥ 100 mm Hg diastolic) at two consecutive visits prior to randomization at Visit 4.
18. Any of the following laboratory criteria: serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $> 3x$ the upper limit of normal (ULN), fasting serum glucose > 200 mg/dL, calculated glomerular filtration rate (GFR) < 30 ml/min, platelet counts $< 60 \times 10^9/L$, or hemoglobin < 10.0 g/dL.
19. Recent history (past 12 months) of drug abuse or alcohol abuse. Alcohol abuse was defined as > 14 drinks per week (1 drink = 12 oz beer, 5 oz wine, or 1.5 oz hard liquor).
20. Exposure to any investigational product within 4 weeks prior to Visit 1, or prior to randomization.
21. Presence of any other condition the Investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

Prohibited Medications

Use of the following medications was prohibited during the study at any time after Visit 1:

- Bile acid sequestrants, fibrates, niacin (other than niacin-containing multiple vitamins < 200 mg), omega-3 drugs or supplements.
- Dietary fiber supplements, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols.
- Oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/asthma) or anabolic steroids.
- Anticoagulants (e.g. warfarin [Coumadin], coumarin, heparin, enoxaparin, clopidogrel).

Permitted Medications

- Statins, CAI or statin-CAI combinations (could not be started at any time after Visit 1).
- Estrogens (other than topical estrogens for local vaginal symptoms), progestins and androgens (could not be started at any time after Visit 1).
- Tamoxifen (could not be started at any time after Visit 1).

Patients could continue use of statins or CAIs or their combination during the study, provided they were on a stable dose for at least 4 weeks prior to Week -4 (Visit 1), and before randomization, and did not change the dose or discontinue the medication during the study.

For patients who required adjustment or addition of permitted statin, CAI or their combination at screening (for example, after discontinuation of omega-3 drugs/supplements), their dose needed to be stable for at least 6 weeks prior to Week -2 (Visit 2) and before randomization, and must not have changed or be discontinued during the study.

Schedule of Visits and Procedures

The following table summarizes the schedule of clinical assessments and procedures.

Table 10: Schedule of Procedures

Study Period	Screen, Washout and Diet Lead-In			Randomization	Treatment			
	1	2	3		4	5	6	7
Visit	-8/-	-2	-1	0	4	8	10	12/ET
Week		±2	±2	±2	±2	±2	±2	±2
Window (days)								
Informed Consent	X							
Medical History	X	X	X	X				
Prior Medications (12 weeks prior to Visit 1)	X	X	X	X				
Clinical Assessments ³	X	X	X	X				X
Physical Examination			X					X
ECG			X					X
Fasting Serum Chemistry ³		X						X
Hemoglobin A _{1c} ⁴	X	X						X
Hematology ⁵		X						X
PT, PTT		X						X
Urinalysis ⁶		X						X
TSH		X						
Urine Pregnancy Test ⁷		X						X
Fasting Lipid Panel ⁸	X	X	X	X	X	X	X	X
Fasting Special Lipid Markers ⁹			X	X				X
Serum Samples for Storage ¹⁰			X	X				X
Fasting Plasma Fatty Acids ¹¹				X				X
hs-CRP			X	X			X	X
TLC Diet Counseling	X	X	X	X	X	X	X	X
TLC Diet Compliance		X	X	X	X	X	X	X
Pancreatitis Counseling	X			X				
Concomitant Medications					X	X	X	X
Adverse Events					X	X	X	X
Eligibility Review	X	X	X	X				
Randomization				X				
Dispense Investigational Product ¹²				X	X	X ¹³	X ¹³	
Investigational Product Compliance					X	X	X	X

ET = Early Termination.

Source EVOLVE study report, Table 9.5.1, pg. 33. Footnotes for Schedule of Procedures:

1 For subjects previously on omega-3 drugs/supplements who need to washout or subjects who require statin/CAI/statin-CAI dose adjustment or addition, Visit 1 is at Week -8. All other subjects, including subjects who are on a stable dose of statin, CAI or statin-CAI at least 4 weeks before screening, or who need to washout of bile acid sequestrants, fibrates, niacin and other lipid-altering supplements, Visit 1 is at Week -4.

2 Includes height and body mass index (BMI) calculation at Visit 1 only; weight, blood pressure and heart rate.

3 Serum chemistry includes sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, phosphate, total protein, albumin, creatine kinase, AST, ALT, alkaline phosphatase, total bilirubin and GFR (calculated only at Visit 2).

4 HbA1c at Visit 1 for subjects with a history of diabetes; at Visit 2 for all other subjects; at Visit 8/ET for all subjects.

5 Hematology includes hemoglobin, hematocrit, white blood cell count and differential, and platelet count.

6 Urine chemical analysis including glucose, bilirubin, ketone, specific gravity, pH, blood, protein, urobilinogen, nitrite, and leukocyte esterase.

7 Females of childbearing potential only.

8 Lipid panel includes serum TG, total cholesterol, direct LDL-C, HDL-C, calculated non-HDL-C, VLDL-C and TC:HDL-C ratio. Serum TG may be repeated, within a timeframe that allows results before randomization.

9 Special lipid markers include serum Apo A-I, Apo B, Apo C-III, RLP-C, Lp-PLA2 and lipoprotein particles (sizes, concentrations and subfractions for VLDL-C, LDL-C and HDL-C).

10 Serum samples to be stored for possible future analysis of non-genetic indicators of metabolic function and/or cardiovascular disease risk.

11 Plasma fatty acids include EPA, DHA and AA.

12 Initial dose to be taken at any time after fasting blood draws; on clinic days, dose to be taken from the newly dispensed kit, at any time after the fasting blood draws.

13 At Visits 6 and 7 (Weeks 8 and 10), only 2 blister packs (two weeks of dosing) were dispensed.

Analysis Populations

The intent-to-treat (ITT) population comprised all patients who were randomized.

The mITT population included all patients who received at least one dose of investigational product and had at least one post-randomization efficacy assessment.

The Per Protocol (PP) population was a subset of the ITT population. Patients were excluded from the PP population for the following reasons and for other reasons as determined prior to the database lock:

- Violations of Inclusion or Exclusion Criteria that could influence the evaluation of the efficacy outcomes.
- Other protocol deviations that would confound the evaluation of efficacy outcomes.
- Non-compliance by the patient, including, but not limited to:
 - Less than 80% overall compliance with study drug consumption, or
 - Use during the study of prohibited drugs or any products thought to alter the primary efficacy outcome.
- Early discontinuation of study or investigational product before Visit 8.

The safety population comprised all patients who received at least one dose of study drug.

Primary and Secondary Efficacy Analysis

The primary endpoint variable for each arm was the percent change in TG levels from Baseline (average of Weeks -2, -1 and 0) to the End of Treatment (average of Weeks 10 and 12). All repeat testing was included in the baseline average.

The secondary endpoint variables for each arm included the percent change from Baseline (average of Weeks -2, -1 and 0) to End of Treatment (average of Weeks 10 and 12) in non-HDL-C and HDL-C. All repeat testing was included in the baseline average.

The primary and secondary efficacy endpoints for each Epanova arm were compared to placebo using ANCOVA, with baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model.

For the primary and secondary endpoints, comparisons of each Epanova group to placebo were made at a significance level of alpha = 0.05, two sided with alpha adjustment for multiple comparisons using Dunnett’s procedure for the primary comparisons and Hommel’s procedure for the secondary comparisons.

6.1.2 Demographics

Demographics were very similar across the 4 treatment groups, approximately 72-80% were men, mean age was approximately 51-53 years, and approximately 89-96% of the population was Caucasian. The use or non-use of statins/ezetimibe was very similar among the four treatment groups with approximately 35% of patients using a statin +/- ezetimibe concomitant medication. Approximately 37% of the overall study population had diabetes at Baseline.

Table 11: Demographics and Baseline Characteristics, mITT Population, EVOLVE study

Characteristic	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99	Total N=393
Age (years)					
Mean (SD)	51 (11)	51(10)	51 (9)	53 (11)	52 (10)
P-value					0.487
Age group (n, %)					
<65 years	87 (89%)	91 (92%)	93 (96%)	83 (84%)	354 (90%)
>65 years	11 (11%)	8 (8%)	4 (4%)	16 (16%)	39 (10%)
P-value					0.036
Sex (n,%)					
Male	76 (78%)	79 (80%)	75(78%)	71 (72%)	301(77%)
Female	22 (22%)	20 (20%)	22 (22%)	28 (28%)	92 (23%)
P-Value					0.581
Race (n, %)					
White/Caucasian	94 (96%)	92 (93%)	88 (91%)	88 (89%)	362 (92%)
African American	0	0	1 (1%)	2 (2%)	3 (0.8%)
Asian	4 (4%)	5 (5%)	6 (6%)	8 (8%)	23 (5.8%)
Diabetes status (n, %)					
Yes diabetes	30 (30.6%)	37 (37.4%)	43 (44.3%)	37 (37.4%)	147 (37.4%)
No diabetes	68 (69.4%)	62 (62.6%)	54 (55.7%)	62 (62.6%)	246

Characteristic	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99	Total N=393
					(62.6%)
P-Value					0.270
Statin Use (n, %)					
No	65 (66%)	64 (65%)	63 (65%)	63 (64%)	255 (65%)
Yes	33 (34%)	35 (35%)	34 (35%)	36 (36%)	138 (35%)
Body mass index (kg/m²)					
Mean (SD)	30.4 (4.35)	31.4 (4.84)	31.7 (4.06)	31.0 (5.07)	31.1 (4.61)
P-value					0.216

Subjects may have reported more than one race or ethnicity.

P-value for continuous variables were generated by one-way ANCOVA with treatment as a factor. P-values for gender, age group, ethnicity, and diabetes were generated using Chi-square test.

Source: Applicant, Jan. 2014 SN 0015.

Table 12: Baseline Lipid Parameters, mITT Population, EVOLVE study

Characteristic	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99	Total N=393
TG (mg/dL)					
Mean (SD)	788.5 (305.11)	790.1 (269.01)	820.4 (353.15)	783.6 (335.21)	795.6 (316.18)
Median	682.3	717.0	728.0	655.0	694.3
P-Value					0.846
non-HDL-C (mg/dL)					
Mean (SD)	220.2 (54.37)	221.0 (62.30)	228.3 (74.10)	235.3 (72.77)	226.2 (66.39)
Median	214.5	205.3	215.3	225.0	217.0
P-Value					0.416
VLDL-C (mg/dL)					
Mean (SD)	139.0 (51.52)	137.9 (56.45)	143.6 (71.46)	143.9 (66.92)	141.1 (61.89)
Median	124.5	123.3	124.0	126.0	124.0
P-Value					0.864

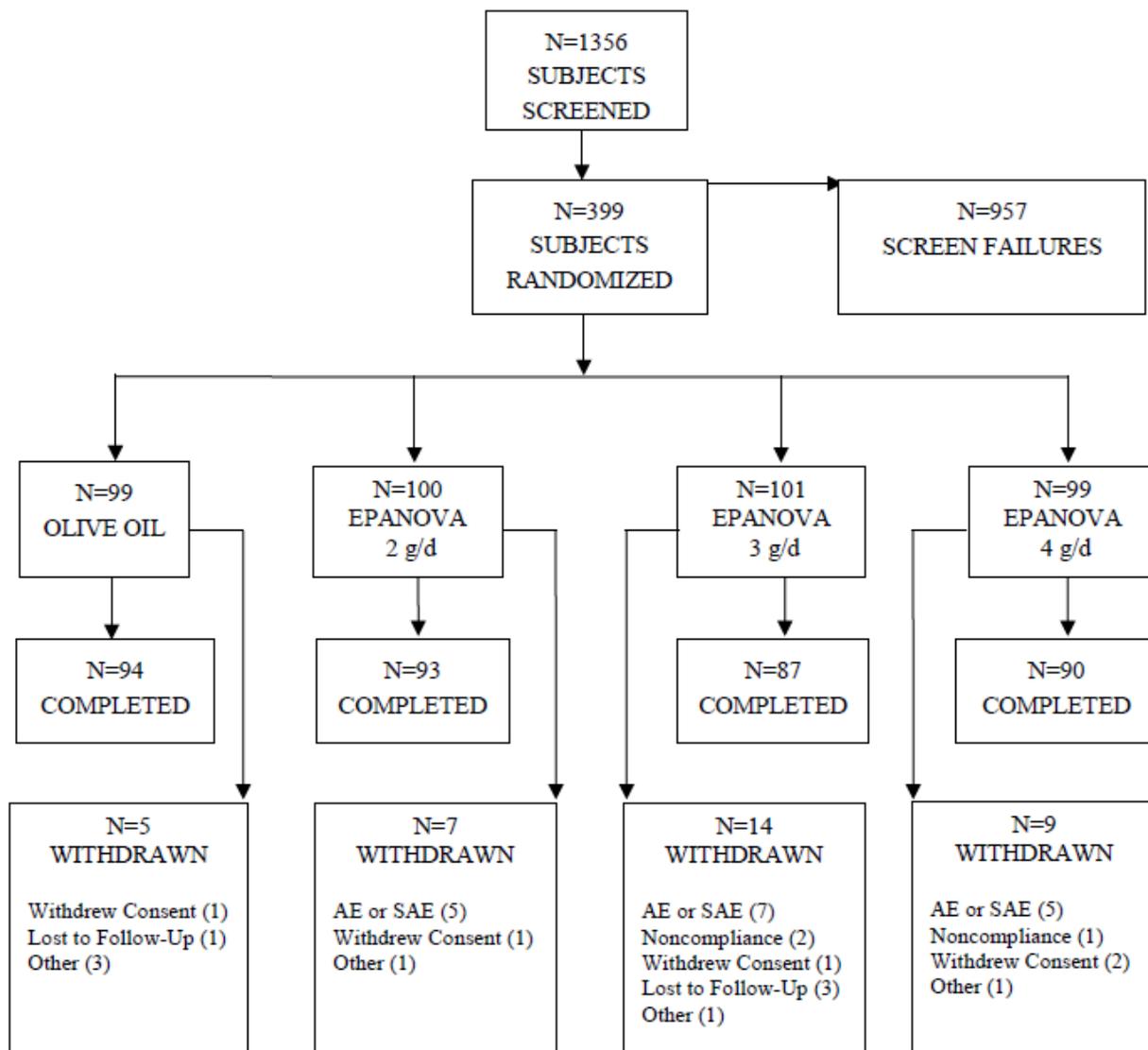
Characteristic	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99	Total N=393
LDL-C (mg/dL)					
Mean (SD)	81.5 (31.49)	83.0 (32.86)	84.7 (38.74)	90.3 (38.86)	84.9 (35.66)
Median	78.2	77.3	81.0	90.3	81.3
P-Value					0.274
HDL-C (mg/dL)					
Mean (SD)	29.2 (7.93)	28.0 (6.87)	29.0 (7.93)	29.9 (9.22)	29.0 (8.03)
Median	28.7	27.3	28.0	28.7	28.0
P-Value					0.338
Total Cholesterol					
Mean (SD)	249.4 (56.82)	249.0 (62.98)	257.4 (73.80)	265.3 (73.14)	255.3 (67.13)
Median	245.5	240.7	243.7	254.3	245.7
P-Value					0.328

Source: Applicant, Jan 2014,SN0015.

Baseline lipid parameters were similar across the four treatment arms. Overall, the median TG was 796 mg/dL, mean LDL-C was 85 mg/dL, and mean HDL-C was 29 mg/dL.

6.1.3 Subject Disposition

Figure 9: Patient Disposition Diagram, EVOLVE study



Source: EVOLVE study report, pg.44.

As shown in the figure above, there were 957 screen failures. The majority (69%) were due to TG levels being out of the acceptable inclusion range (≥ 500 mg/dL and < 2000 mg/dL). The next most prevalent reason for screen failure was other laboratory abnormality (24%) with uncontrolled diabetes (HbA1c $\geq 9\%$) having the greatest occurrence.

Each of the four treatment arms had high percentage of study completers: 95% for placebo, 93% for Epanova 2g, 86% for Epanova 3g, and 91% for Epanova 4g. As

shown in the table below, there were no statistically significant differences between the treatment arms in terms of the percentage of patient discontinuations (p=0.146).

Table 13: Summary Table of Patient Disposition

	Olive Oil N (%)	Epanova 2 g N (%)	Epanova 3 g N (%)	Epanova 4 g N (%)	Total N (%)	p-value ¹
Total Randomized					399	
Completed Study	94 (94.9%)	93 (93.0%)	87 (86.1%)	90 (90.9%)	364 (91.2%)	
Discontinued Study	5 (5.1%)	7 (7.0%)	14 (13.9%)	9 (9.1%)	35 (8.8%)	0.146
Primary Reason for Discontinuation						
AE or SAE	0 (0.0%)	5 (5.0%)	7 (6.9%)	5 (5.1%)	17 (4.3%)	
Non-compliance	0 (0.0%)	0 (0.0%)	2 (2.0%)	1 (1.0%)	3 (0.8%)	
Pregnancy	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Withdrew Consent	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	5 (1.3%)	
Lost to Follow-Up	1 (1.0%)	0 (0.0%)	3 (3.0%)	0 (0.0%)	4 (1.0%)	
Other ²	3 (3.0%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	6 (1.5%)	
Source: Table 14.1.1.1.						
Percentages are calculated as % = n/N.						
¹ p-value from Chi-Square Test.						
² “Other” refers to withdrawal from an expected laboratory abnormality in subjects with dyslipidemia that did not result in an adverse event as defined in the protocol.						

Source: EVOLVE study report, pg. 45.

Thirty-five patients among the four treatment groups discontinued the study, 17 because of an AE or SAE and 18 for other reasons. While the placebo, 2 g Epanova and 4 g Epanova groups had similar withdrawals (5 to 9 subjects) the 3 g Epanova group had a greater number of discontinuations (14 subjects). However, the p-value for discontinuations was not statistically significant at p=0.146.

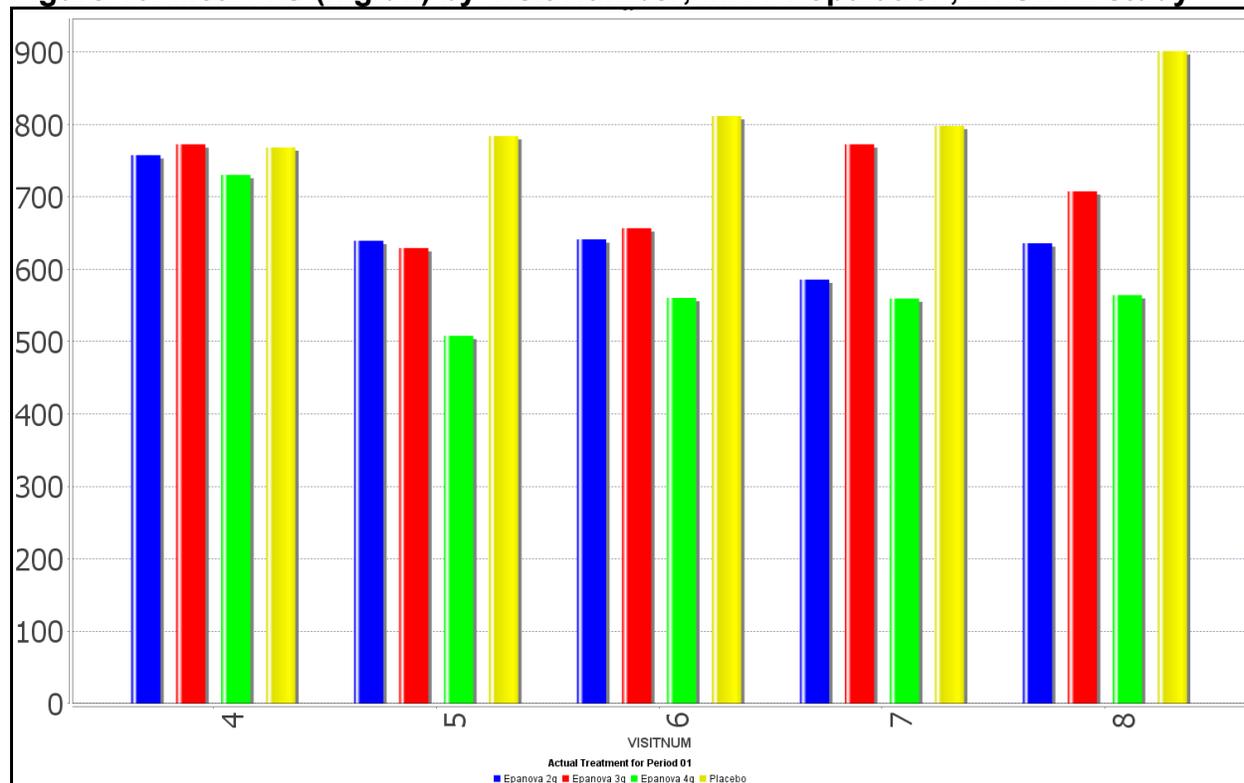
Discontinuations in the placebo group were primarily due to consent withdrawal, lost to follow-up and laboratory abnormalities; however, the Epanova groups had discontinuations primarily from adverse events that were gastrointestinal in nature.

6.1.4 Analysis of Primary Endpoint(s)

The primary analysis was conducted with the modified ITT population (mITT). Greater than 98% of the patients were included in this category (i.e., all patients who received at least one dose of investigational product and had at least one post-randomization efficacy assessment). For instance, all patients in the 4 g Epanova group were included in the mITT population, only one patient was removed in each of the placebo and 2 g Epanova groups, and four patients were removed from the 3 g Epanova group.

The following figure shows the mean TG (mg/dL) at Randomization, Week 4, Week 8, Week 10 and Week 12/ Early Termination by the four treatment arms.

Figure 10: Mean TG (mg/dL) by Visit Number, mITT Population, EVOLVE study

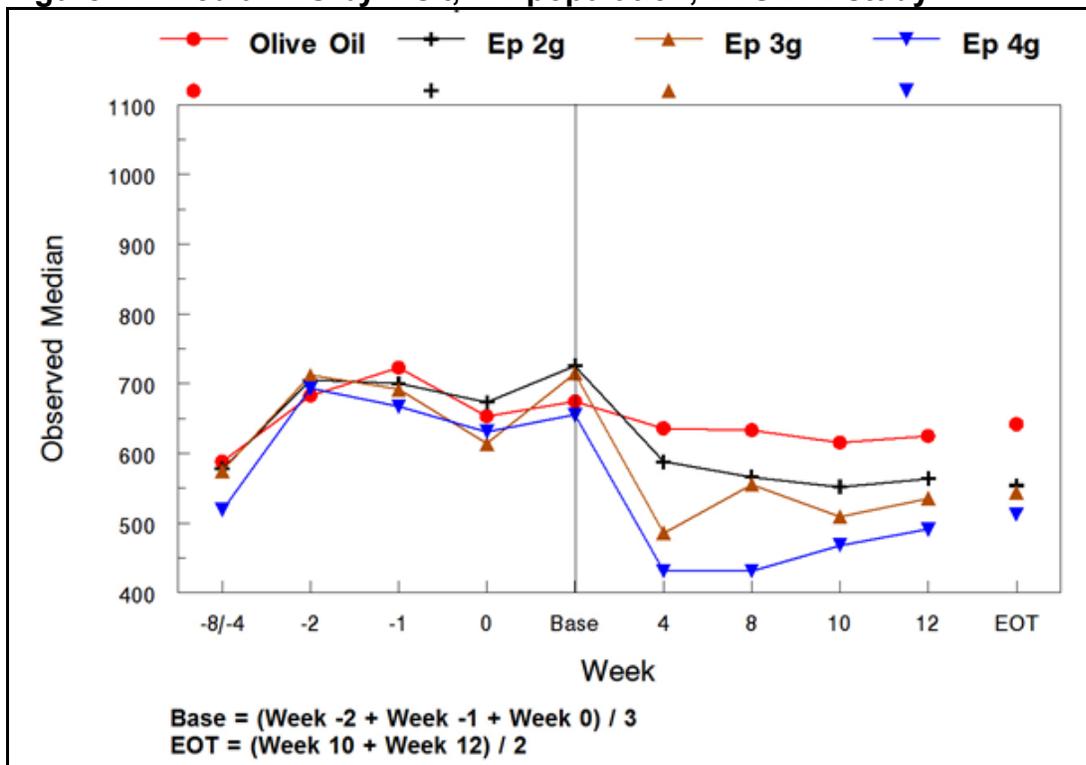


Legend: Epanova 2g=Blue, Epanova 3g=Red, Epanova 4g=Green, Placebo =Yellow.
 Visit 4=Randomization, Visit 5= Week 4, Visit 6=Week 8, Visit 7=Week 10, Visit 8=Week12/ET

Treatment effect was noticeable four weeks after randomization in all three Epanova treatment arms. However, TG levels were more variable with Epanova 3g during the course of the study.

The following figure shows the median TG by visit during the course of the EVOLVE trial.

Figure 11: Median TG by Visit, ITT population, EVOLVE study

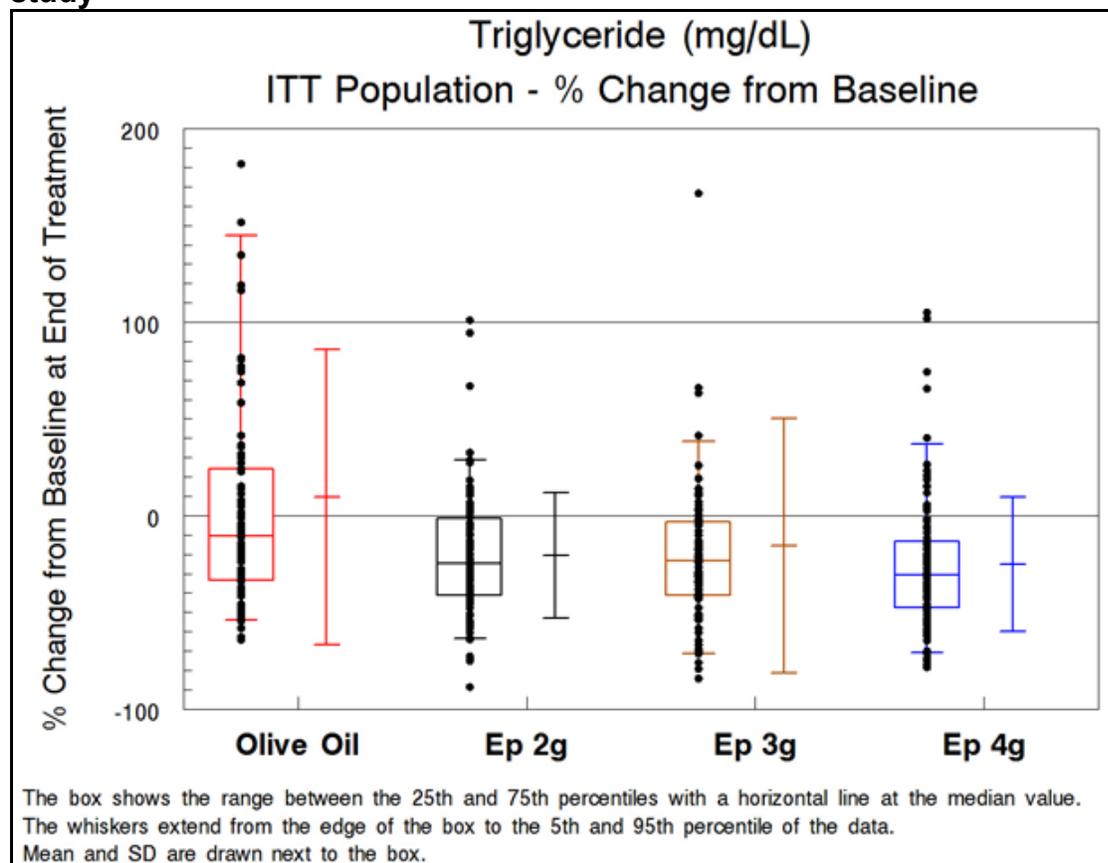


Source: Dr. Cynthia Liu, statistical reviewer

Epanova 4g initially showed the most TG reduction at Week 4 and 8. However, at later time points, the median TG level drifted up until by the end of the study at Week 12/ End of Trial, TG reduction with Epanova 4g was very similar to that achieved by Epanova 2g and 3g.

The following figure summarizes TG percent change from Baseline.

Figure 12: Percent Change from Baseline in TG (mg/dL), ITT population, EVOLVE study*



Source: Dr. Cynthia Liu, statistical reviewer. Values above 200% are truncated from this figure.

As shown by the box-whiskers plot above, there is very little difference in percent change from Baseline between the three doses of Epanova.

The following table shows the results for TG for the mITT population.

Table 14: Baseline and Percent Change from Baseline to Endpoint in TG- mITT Population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	788.5 (305.11)	790.1 (269.01)	820.4 (353.15)	783.6 (335.21)

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Median	682.3	717.0	728.0	655.0
Percent Change from Baseline²				
N	98	95	94	95
Mean (SD)	9.5 (76.32)	-20.7 (32.37)	-15.5 (65.89)	-25.0 (34.72)
Median	-10.4	-24.5	-23.4	-30.7
LSM³, (95%CI)	-4.26% (-13.07, 5.44)	-25.94% (-32.84,-18.33)	-25.46% (-32.44, -17.75)	-30.86% (-37.32,-23.74)
LSM, difference from Placebo (95% CI)		-21.68% (-40.70, -2.89)	-21.19% (-40.32, -2.29)	-26.60% (-45.12,-8.38)
P-value⁴		0.005 ^r	0.007 ^r	<0.001 ^r

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.

[r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.1, pg. 49.

The baseline TG mean values ranged from approximately 784 to 820 mg/dL across the four treatment groups in the mITT population while the median values ranged from 655 to 728 mg/dL.

Although all three doses of Epanova decreased TG, the result for the 3 g dose was numerically similar to the 2g dose. The LSM percent change from baseline for the 2 g dose was -25.94% as compared to -25.46% for the 3 g dose, and the LSM difference from placebo was -21.68% for 2 g Epanova and -21.19% for 3 g Epanova. Therefore there was no benefit of 3 g over 2 g for TG reduction.

Patients in the 4g Epanova treatment arm achieved a LSM difference from placebo of -26.60%, only 5% greater TG reduction than that achieved by patients on the 2g Epanova dose. I do not know whether this 5% greater TG reduction is clinically meaningful given that TG is highly variable.

Furthermore, the 95% CI for the LSM change from baseline for the 4g dose substantially overlaps the 95% CI for the 2g dose, demonstrating that results achieved with the 2g dose are similar to those achieved with the 4g dose. Therefore, statistically, it is difficult to distinguish between the 2g and 4g dose results as evidenced by the overlap of the confidence intervals.

The following table summarizes the TG-lowering effect and EPA concentrations by the four treatment arms in the EVOLVE trial.

Table 15: Epanova Dose, TG-Lowering Effect, and EPA Concentrations, EVOLVE study

	Olive Oil	Epanova 2g	Epanova 3g	Epanova 4g
EPA % change from Baseline, LS Mean	15.51	267.04	331.86	406.32
EPA 95% CI	(-3.36, 38.06)	(207.53, 338.08)	(258.51, 420.22)	(323.58, 505.23)
EPA p value⁽¹⁾		< 0.001	< 0.001	< 0.001
TG % change from Baseline, LS Mean	-4.26	-25.94	-25.46	-30.86
TG 95% CI	(-13.07, 5.44)	(-32.84, -18.33)	(-32.44, -17.75)	(-37.32, -23.74)
TG p value⁽¹⁾		0.005	0.007	< 0.001

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons for TG comparing each Epanova vs. Olive Oil.

Source: Applicant, email submission on 2/18/2014.

The following table summarizes the TG-lowering effect and DHA concentrations by the four treatment arms in the EVOLVE trial.

Table 16: Epanova Dose, TG-Lowering Effect, and DHA Concentrations, EVOLVE study

	Olive Oil	Epanova 2g	Epanova 3g	Epanova 4g
DHA % change from Baseline, LS Mean	6.21	56.72	64.07	71.77
DHA 95% CI	(-3.30, 16.66)	(42.76, 72.04)	(48.73, 81.00)	(56.34, 88.71)
DHA p value⁽¹⁾		< 0.001	< 0.001	< 0.001
TG % change from Baseline, LS Mean	-4.26	-25.94	-25.46	-30.86

	Olive Oil	Epanova 2g	Epanova 3g	Epanova 4g
TG 95% CI	(-13.07, 5.44)	(-32.84, -18.33)	(-32.44, -17.75)	(-37.32, -23.74)
TG p value ⁽¹⁾		0.005	0.007	< 0.001

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons for TG comparing each Epanova vs. Olive Oil.

Source: Applicant, email submission on 2/18/2014.

The applicant argues that the 2g dose has potent effectiveness because of the increased bioavailability of the formulation and that the 2g dose is equivalent to higher doses of other omega-3 products. I would agree that this is true and also applies to the higher doses of Epanova; that is the 2g dose of Epanova is as potent, with respect to its TG-lowering effect, as the 3g and 4g dose of Epanova.

Change in TG by Categorical Achievement TG <500 mg/dL

In terms of the number and percentage of patients who achieved the treatment goal of TG<500 mg/dL at the end of the 12-week trial, there were no statistically significant differences between the four treatment groups (including placebo) in the Chi-square analysis (see table below).

Table 17: Patients Who Achieved TG <500 mg/dL at End of Treatment, mITT Population, EVOLVE study

TG<500 mg/dL	Placebo N=98	Epanova 2 g N=95	Epanova 3 g N=94	Epanova 4 g N=95
Yes, n (%)	36 (37%)	37 (39%)	42 (45%)	49 (52%)
No, n (%)	62 (63%)	58 (61%)	52 (55%)	46 (28%)
P-value	0.160			

Source: EVOLVE study report, Table 11.4.13, pg. 76.

Change in TG by Baseline TG <750 mg/dL or ≥750 mg/dL

In patients with baseline TG <750 mg/dL, the LS mean difference from placebo in percent change from baseline was approximately -14% for Epanova 2 g, -18% for Epanova 3 g, and -20% for Epanova 4g. The LS mean percent change from Baseline for the 2 g dose of Epanova was not statistically significantly different from placebo.

Table 18: Change from Baseline to Endpoint, Patients with Baseline TG <750

	Placebo N=59	Epanova 2 g N=54	Epanova 3 g N=52	Epanova 4 g N=64
Baseline¹				
Mean (SD)	596.8 (76.14)	592.8 (84.09)	581.2 (88.65)	588.6 (82.12)
Median	599.3	603.8	571.0	587.2
Percent Change from Baseline²				
Mean (SD)	-1.2 (45.86)	-17.1 (29.09)	-22.0 (28.51)	-24.3 (25.34)
Median	-11.1	-16.3	-24.1	-24.7
LSM³, (95%CI)	-9.01 (-18.25, 1.29)	-22.58 (-30.94, -13.20)	-26.58 (-34.56, -17.63)	-28.61 (-35.66, -20.79)
LSM, difference from Placebo (95% CI)		-13.57 (-34.95, 7.77)	-17.57 (-38.52, 3.27)	-19.60 (-39.50, -0.07)
P-value⁴		0.410 [r]	0.034 [r]	0.013 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.

[r] indicates data were ranked prior to performing ANCOVA.

Source: Applicant, Jan 2014, SN0015

In patients with baseline TG \geq 750 mg/dL, the LS mean difference from placebo in percent change from baseline was approximately -33% for Epanova 2 g, -27% for Epanova 3 g, and -36% for Epanova 4g.

Table 19: Change from Baseline to Endpoint, Patients with Baseline TG \geq 750 mg/dL

	Placebo N=39	Epanova 2 g N=45	Epanova 3 g N=45	Epanova 4 g N=35
Baseline¹				
Mean (SD)	1078.5 (292.33)	1026.9 (217.97)	1096.9 (342.27)	1140.2 (329.94)

	Placebo N=39	Epanova 2 g N=45	Epanova 3 g N=45	Epanova 4 g N=35
Median	1004.7	990.3	989.7	1051.3
Percent Change from Baseline²				
Mean (SD)	25.8 (105.87)	-24.9 (35.69)	-8.1 (91.43)	-26.3 (47.58)
Median	-8.7	-33.1	-22.4	-38.7
LSM³, (95%CI)	2.12 (-14.59, 22.09)	-31.02 (-41.78, -18.27)	-24.46 (-36.24, -10.50)	-33.56 (-45.32, -19.28)
LSM, difference from Placebo (95% CI)		-33.14 (-68.51, 0.56)	-26.57 (-63.10, 8.53)	-35.68 (-72.16, -0.17)
P-value⁴		0.006 [r]	0.172 [r]	0.002 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: Applicant, Jan 2014, SN0015

Reviewer Comment: The magnitude of TG lowering with Epanova appears to be greater in patients with higher baseline TG, i.e. patients with baseline TG \geq 750 mg/dL.

6.1.5 Analysis of Secondary Endpoints(s)

Non-HDL-C

The following table summarizes the results for non-HDL-C in the mITT population.

Table 20: Baseline and Percent Change from Baseline to Endpoint in non-HDL-C, mITT population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
N	98	99	97	99
Mean (SD)	220.2 (54.37)	221.0 (62.30)	228.3 (74.10)	235.3 (72.77)
Median	214.5	205.3	215.3	225.0
Percent Change from Baseline²				
N	98	95	94	95
Mean (SD)	7.5 (37.43)	-5.2 (19.62)	-3.9 (28.10)	-7.9 (19.63)
Median	-0.9	-7.7	-3.6	-7.7
LSM³, (95%CI)	2.53 (-2.31, 7.61)	-7.61 (-12.02, -2.97)	-6.89 (-11.35, -2.21)	-9.63 (-13.95, -5.09)
LSM, difference from Placebo (95% CI)		-10.14 (-21.01, 0.71)	-9.42 (-20.34, 1.48)	-12.16 (-22.92, -1.43)
P-value⁴		0.017 [r]	0.019 [r]	0.001 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

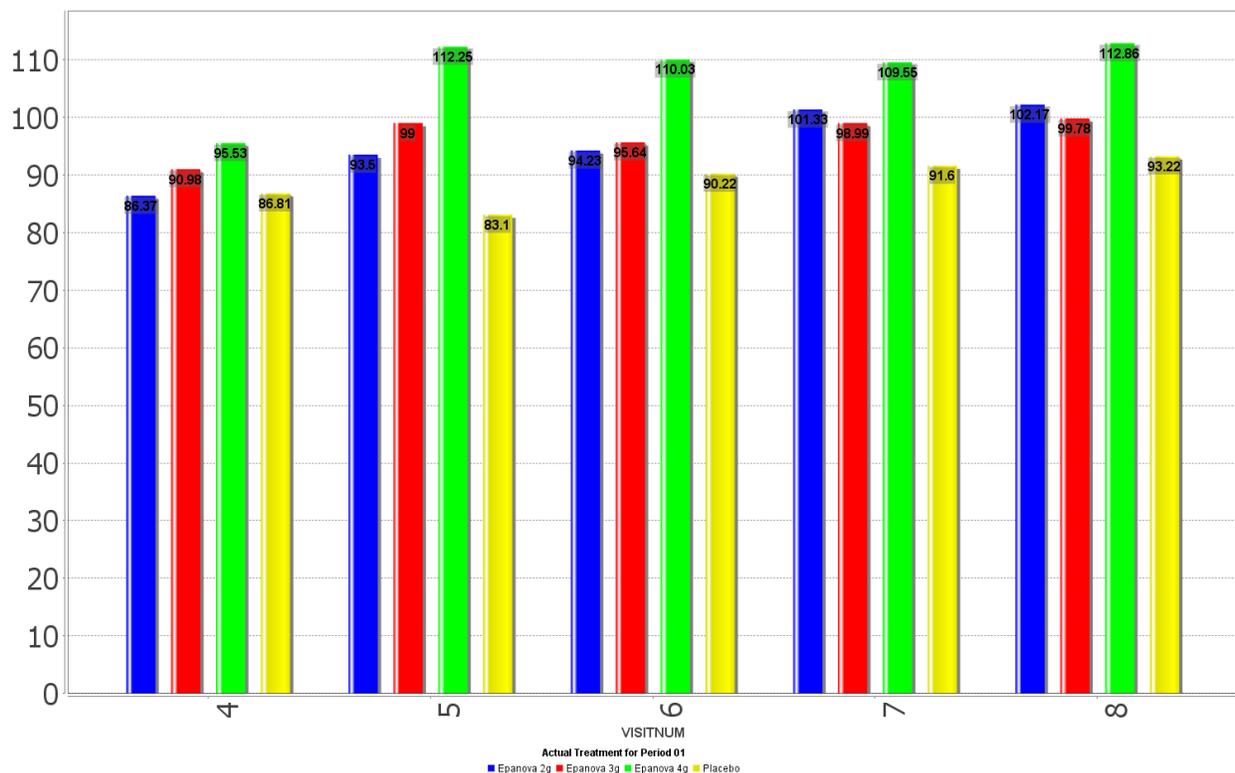
Source: EVOLVE study report, Table 11.4.2, pg. 53.

The baseline mean and median non-HDL-C values were generally similar across the 4 treatment groups ranging from approximately 220 to 235 mg/dL for mean values and from 205 to 225 mg/dL for median values, respectively.

According to the applicant, the non-HDL-C data were not normally distributed, and the tests of significance were performed after rank transformation of percent change values. Relative to placebo, the percent reductions were -10% for 2 g Epanova, -9% for 3 g Epanova and -12% for 4 g Epanova. Similar to TG, for non-HDL-C, the 3 g Epanova dose was numerically inferior to the 2 g Epanova dose.

Reviewer Comment: Epanova 4g resulted in an approximate 2% greater non-HDL-C reduction than that achieved with Epanova 2g dose. The 3g dose result for non-HDL-C was not impressive, approximately 0.72% less than that achieved with the 2g dose.

LDL-C



The following table summarizes the results for LDL-C in the mITT population.

Table 21: Baseline and Percent Change from Baseline to Endpoint in LDL-C, mITT Population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	81.5 (31.49)	83.0 (32.86)	84.7 (38.74)	90.3 (38.86)
Median	78.2	77.3	81.0	90.3

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Percent Change from Baseline²				
N	98	95	94	95
Mean (SD)	11.7 (38.39)	25.5 (32.69)	20.3 (31.66)	26.2 (35.80)
Median	9.8	21.4	16.6	26.2
LSM³, (95%CI)	3.0 (-2.93, 9.30)	19.20 (12.26, 26.58)	14.25 (7.57, 21.35)	19.35 (12.39, 26.75)
LSM, difference from Placebo (95% CI)		16.20 (1.05, 31.44)	11.25 (-3.60, 26.16)	16.35 (1.17, 31.61)
P-value⁴		0.003 [r]	0.072 [r]	<0.001 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.4, pg. 58.

The baseline mean LDL-C values were similar across the four treatment groups ranging from approximately 82 to 90 mg/dL. The LSM difference from placebo analyses demonstrated statistically significant percent increases in LDL-C from baseline of approximately 16.2%, 11.3% and 16.35%, in the 2 g, 3 g and 4 g Epanova groups, respectively.

Reviewer Comment: The absolute atherogenic potential of the increase in LDL-C seen with Epanova treatment in patients with severe hypertriglyceridemia is unknown. The applicant proposes that as Apo-CIII production is decreased with Epanova treatment, there is increased lipolysis of TG-rich VLDL and conversion to IDL-C and LDL-C. Furthermore, these LDL-C particles are more buoyant and less atherogenic. Although there is an increase in LDL-C, there was an overall reduction of non-HDL-C, relative to placebo, with Epanova treatment. The effect of these changes on cardiovascular risk has not been determined in a cardiovascular outcomes trial..

HDL-C

The following table summarizes the results for HDL-C in the mITT population.

Table 22: Baseline and Percent Change from Baseline to Endpoint in HDL-C in mITT population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	29.2 (7.93)	28.0 (6.87)	29.0 (7.93)	29.9 (9.22)
Median	28.7	27.3	28.0	28.7
Percent Change from Baseline²				
N	98	95	94	95
Mean (SD)	5.1 (29.94)	9.8 (22.22)	6.0 (19.69)	7.3 (17.88)
Median	2.2	7.0	6.9	5.0
LSM³, (95%CI)	1.92 (-1.98, 5.98)	7.35 (3.18, 11.68)	3.78 (-0.27, 7.99)	5.77 (1.65, 10.06)
LSM, difference from Placebo (95% CI)		5.42 (-4.00, 14.86)	1.86 (-7.42, 11.14)	3.85 (-5.51, 13.23)
P-value⁴		0.076 [r]	0.091 [r]	0.091 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.3, pg 55.

The baseline mean HDL-C values were generally similar across the 4 treatment groups ranging from approximately 28 to 30 mg/dL.

Relative to placebo, there were numerical percent increases of HDL-C from baseline in each of the Epanova groups, however, none of the changes were statistically significant (p-values on ranked data of 0.076, 0.091 and 0.091, respectively versus placebo).

VLDL-C

The following table summarizes the results for VLDL-C in the mITT population.

Table 23: Baseline and Percent Change from Baseline to Endpoint in VLDL-C mITT Population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	139.0 (51.52)	137.9 (56.45)	143.6 (71.46)	143.9 (66.92)
Median	124.5	123.3	124.0	126.0
Percent Change from Baseline²				
N	98	95	94	95
Mean (SD)	2.7 (63.74)	-20.7 (31.58)	-19.6 (39.60)	-27.3 (30.67)
Median	-11.3	-24.7	-21.6	-34.7
LSM³, (95%CI)	-8.52 (-16.58, 0.31)	-26.55 (-33.11, -19.36)	-26.44 (-33.03, -19.20)	-32.98 (-38.97, -26.41)
LSM, difference from Placebo (95% CI)		-18.03 (-35.66, -0.58)	-17.92 (-35.59, -0.42)	-24.46 (-41.45, -7.72)
P-value⁴		0.007 [r]	0.006 [r]	<0.001 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.

[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).

[3] LSM and LSM differences from the ANCOVA model using natural log transformed data.

[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.

[r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.4, pg. 59.

The baseline mean VLDL-C ranged from approximately 138 to 144 mg/dL across the four treatment groups. The LSM analyses demonstrated statistically significant percent decreases in VLDL-C from baseline of approximately -26.6%, -26.4% and -33.0%, in the 2 g, 3 g and 4 g Epanova groups, respectively; whereas the placebo group showed an approximate - 8.5% decrease that was not significant.

Relative to the placebo group, the percent reductions of VLDL-C in each of the Epanova groups were significant (-18.0%, -17.9% and -24.5%, respectively; p-values on ranked data of 0.007, 0.006 and <0.001, respectively).

Reviewer Comment: Epanova 2g and 3g achieved equivalent reductions in VLDL-C. Epanova 4g resulted in an approximate 6.43% greater LSM difference from placebo as compared to Epanova 2g.

Total Cholesterol

The following table summarizes the results for TC in the mITT population.

Table 24: Baseline and Percent Change from Baseline to Endpoint in Total Cholesterol, mITT Population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	249.4 (56.82)	249.0 (62.98)	257.4 (73.80)	265.3 (73.14)
Median	245.5	240.7	243.7	254.3
Percent Change from Baseline²				
N	98	95	94	95
Mean (SD)	7.0 (32.21)	-3.6 (16.81)	-2.6 (24.85)	-6.3 (17.43)
Median	-0.3	-6.4	-2.9	-6.2
LSM³, (95%CI)	3.17 (-0.99, 7.51)	-5.44 (-9.30, -1.42)	-4.85 (-8.74, -0.79)	-7.46 (-11.24, -3.52)
LSM, difference from		-8.61 (-17.99, 0.75)	-8.02 (-17.43, 1.38)	-10.63 (-19.92, -1.36)

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Placebo (95% CI)				
P-value⁴		0.037 [r]	0.083 [r]	0.003 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.4, pg. 58.

The baseline mean TC values were generally similar across the four treatment groups, ranging from approximately 249 to 265 mg/dL. The LSM analyses demonstrated significant (95% CI) percent decreases in TC from baseline of approximately -5.4%, -4.9% and -7.5%, in the 2 g, 3 g and 4 g Epanova groups, respectively; whereas the placebo group showed an approximate 3.2% increase that was not significant.

Relative to placebo, the percent reductions of TC were statistically significant in the 2 g and 4 g Epanova dose groups only (-8.6% and -10.6%, respectively; p-values on ranked data were 0.037 and 0.003, respectively). The LSM difference from placebo in percent change for the 3 g dose of Epanova was not statistically significant.

Apo B

The following table summarizes the results for Apo B in the mITT population.

Table 25: Baseline and Percent Change from Baseline to End of Treatment in Apo B, mITT Population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	112.2 (25.69)	115.6 (25.93)	114.5 (27.48)	119.3 (28.56)
Median	110	114	112	118
Percent Change from Baseline²				

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
N	92	93	85	92
Mean (SD)	5.0 (29.46)	5.9 (19.32)	4.6 (17.98)	5.7 (20.98)
Median	2.3	6.3	5.6	5.7
LSM³, (95%CI)	0.86 (-3.56, 5.48)	3.84 (-0.65, 8.54)	2.28 (-2.36, 7.15)	3.78 (-0.77, 8.53)
LSM, difference from Placebo (95% CI)		2.99 (-7.45, 13.43)	1.42 (-9.18, 12.05)	2.92 (-7.57, 13.42)
P-value⁴		0.322 [r]	0.798 [r]	0.422 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM and LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

The baseline mean Apo B levels were similar across the four treatment groups ranging from approximately 112 to 119 mg/dL. The LSM analyses demonstrated percent increases in Apo B from baseline of approximately 3.8%, 2.3% and 3.8%, in the 2 g, 3 g and 4 g Epanova groups, respectively, and 0.9% in the olive oil group. Relative to the olive oil group, none of the percent increases in Apo B were significant (p-values on ranked data).

6.1.6 Other Endpoints

Hemoglobin A1c

The applicant conducted efficacy analyses with HbA1c, although changes in HbA1c and fasting glucose are also considered in the safety evaluation (see Section 7).

Historically, some studies have raised concern that omega-3 ethyl ester consumption could increase fasting plasma glucose (FPG) without corresponding increase in HbA1C.¹⁰ However, a recent Cochrane meta-analysis suggested that neither the FPG

10 Balk EM, Lichtenstein AH, Chung M, et al. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis* 2006; 189:19-30.

nor the HbA1c increases with omega-3 ethyl ester therapy.¹¹ Pooled data from the Lovaza NDA datasets (post-hoc) showed a slight increase in median FPG in the Lovaza treatment group (median change +6.5mg/dL) as compared to the placebo group (+2 mg/dL).

The following table summarizes the baseline and changes from baseline for HbA1c for the mITT population.

Table 26: Baseline and Change from Baseline to End of Treatment in Hemoglobin A1c, mITT population, EVOLVE study

	Placebo N=98	Epanova 2 g N=99	Epanova 3 g N=97	Epanova 4 g N=99
Baseline¹ (%)				
N	98	97	96	98
Mean (SD)	6.0 (1.01)	6.1 (0.96)	6.2 (1.02)	6.1 (1.02)
Median	5.7	5.8	5.9	5.7
Absolute Change from Baseline²				
N	91	91	83	90
Mean (SD)	0.1 (0.50)	0.2 (0.43)	0.1 (0.46)	0.1 (0.43)
Median	0.1	0.1	0.1	0.1
P-value		0.951 [r]	>0.999 [r]	>0.999 [r]

SD = Standard Deviation; CI = Confidence Interval
 [1] Baseline = Week -8/-4 for diabetics otherwise Week -2.
 [2] % Change from Baseline to End of Treatment (Week 12).
 [3] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: Applicant Jan 2014, SN0015.

11 Hartweg J, Perera R, Montori VM, Dinneen SF, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database of Systematic Review. 2008, Issue 1. Art. No.: CD003205.DOI: 10.1002/14651858.CD003205.pub2.

Reviewer Comment: Relative to placebo, there were no statistically significant changes in percent change from baseline for HbA1c. However, it is important to note that generalizability is difficult due to the small sample size.

hsCRP

The following table summarizes the baseline and changes from baseline for hs-CRP for the mITT population.

Table 27: Baseline and Percent Change from Baseline in hs-CRP, mITT population, EVOLVE study

	Placebo N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99
Baseline¹ (mg/dL)				
N	98	99	97	99
Mean (SD)	3.7 (4.16)	3.2 (3.12)	4.3 (7.69)	3.9 (6.08)
Median	2.3	2.2	2.1	2.3
Absolute Change from Baseline²				
N	94	93	89	93
Mean (SD)	-0.7 (3.73)	-0.2 (2.34)	-0.5 (3.87)	-0.8 (5.51)
Median	-0.2	0.1	-0.1	-0.3
P-value		0.656 [r]	0.725 [r]	0.985 [r]

SD = Standard Deviation; CI = Confidence Interval

[1] Baseline = Average of Weeks -1 and 0.

[2] End of Treatment = Average of Weeks 10 and 12.

[3] LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change +100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation (SE was not back-transformed).

[4] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. olive oil.

[r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.12, pg. 75.

According to the applicant, relative to placebo, there were no statistically significant changes in hs-CRP in any of the Epanova treatment groups.

6.1.7 Subpopulations

Stratification by Subgroup TG \geq 750 mg/dL or $<$ 750 mg/dL

The following table summarizes the results for the subgroup of patients in the mITT population by baseline TG \geq 750 mg/dL. This was a post-hoc analysis.

Table 28: Percent Change in Lipid Parameters from Baseline to End of Treatment by Subgroup Baseline TG \geq 750 mg/dL, mITT Population, EVOLVE study

	Placebo N=39	Epanova 2 g N=45	Epanova 3 g N=45	Epanova 4 g N=35
Baseline TG \geq750 mg/dL				
Lipid Variable TG				
Baseline Median TG	1004.7	990.3	989.7	1051.3
N	39	44	44	34
LSM, difference from Placebo (95% CI), % Change from Baseline		-33.14 (-68.51, 0.56)	-26.57 (-63.10, 8.53)	-35.68 (-72.16, -0.17)
P-value		0.006 [r]	0.172 [r]	0.002 [r]
Lipid Variable non-HDL-C				
Baseline Mean (SD) Non-HDL-C	242.2 (59.20)	240.9 (78.89)	262.0 (86.50)	272.5 (90.52)
N	39	44	44	34
LSM, difference from Placebo (95% CI), % Change from Baseline		-16.16 (-35.92, 3.31)	-9.51 (-29.87, 10.64)	-15.54 (-36.51, 5.42)
P-value		0.011	0.420	0.031

	Placebo N=39	Epanova 2 g N=45	Epanova 3 g N=45	Epanova 4 g N=35
Lipid Variable HDL-C				
Baseline Mean (SD) HDL-C	27.3 (8.12)	25.0 (5.80)	26.7 (7.09)	25.9 (7.28)
N	39	44	44	34
LSM, difference from Placebo (95% CI), % Change from Baseline		6.88 (-9.56, 23.28)	0.45 (-15.51, 16.35)	6.68 (-10.86, 24.39)
P-value		0.159	0.484	0.199
Lipid Variable LDL-C				
Baseline Mean (SD) LDL-C	66.6 (26.96)	69.5 (34.83)	72.8 (38.42)	72.5 (37.03)
N	39	44	44	34
LSM, difference from Placebo (95% CI), % Change from Baseline		25.88 (-1.22, 53.18)	19.01 (-7.34, 45.48)	29.51 (0.00, 59.87)
P-value		0.065 [r]	0.244 [r]	0.001 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. placebo.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: Applicant Jan 2014, SN0015.

In the baseline TG \geq 750 mg/dL strata, relative to the placebo group, the Epanova groups showed LSM percent TG reductions from baseline of approximately -33%, -27% and -36%, respectively, which were approximately 6-11% greater than the TG reductions in the overall mITT population and significant on ranked data for the 2 g and

4 g doses. The 3g dose of Epanova was not statistically significant for subgroup TG ≥ 750 mg/dL. It is important to point out that the 4g dose provided an approximate 2.54% greater reduction in TG over the 2g dose.

For non-HDL-C, relative to the placebo group, the LSM percent reductions from baseline for the TG ≥ 750 mg/dL subgroup of approximately -16% (in the 2 and 4 g dose) were greater than the overall mITT population of approximately -11% (in the 2 and 4 g dose). The 3g dose of Epanova was not statistically significant for reductions in non-HDL-C in the subgroup TG ≥ 750 mg/dL. The 2g dose provided a numerically greater reduction in non-HDL- C than the 4g dose.

For HDL-C, relative to the placebo group, the LSM percent differences from baseline for the TG ≥ 750 mg/dL subgroup were comparable to the mITT population across the Epanova dose groups and like the mITT population were not statistically significant.

In the baseline TG ≥ 750 mg/dL stratum, , relative to the placebo group, the Epanova 2g and 4g treatment arms showed LSM percent increases from baseline in LDL-C of approximately +26% and +30%, respectively, which was a greater increase than which occurred for the overall mITT population.

Reviewer Comment: In this post-hoc analysis for the subgroup with baseline TG ≥ 750 mg/dL, the magnitudes of TG and non-HDL-C reduction for Epanova appear to be greater than those observed in the overall mITT population. However, the results between the 2g and 4g dose were very similar, with the 4g dose only providing an approximate 2.54% greater reduction in TG than the 2g dose. For non-HDL-C, the 2g was numerically better than the 4g dose.

The following table summarizes the results for the subgroup of patients in the mITT population by baseline TG < 750 mg/dL.

Table 29: Percent Change in Lipid Parameters from Baseline to End of Treatment by Subgroup Baseline TG < 750 mg/dL, mITT Population, EVOLVE study

	Placebo N=59	Epanova 2 g N=54	Epanova 3 g N=52	Epanova 4 g N=64
Baseline TG ≤ 750 mg/dL				
Lipid Variable TG				
Baseline Median TG	599.3	603.8	571.0	587.2
N	59	51	50	61

	Placebo N=59	Epanova 2 g N=54	Epanova 3 g N=52	Epanova 4 g N=64
Baseline TG \leq750 mg/dL				
LSM, difference from Placebo (95% CI)		-13.57 (-34.95, 7.77)	-17.57 (-38.52, 3.27)	-19.60 (-39.50, -0.07)
P-value		0.410 [r]	0.034 [r]	0.013 [r]
Lipid Variable non-HDL-C				
Baseline Mean (SD) Non-HDL-C	205.7 (45.90)	204.4 (37.30)	199.2 (44.89)	215.0 (51.28)
N	59	51	50	61
LSM, difference from Placebo (95% CI)		-5.1 (-12.03, 1.82)	-10.1 (-17.03, -3.08)	-9.7 (-16.40, -3.08)
P-value		0.148	0.010	0.009
Lipid Variable HDL-C				
Baseline Mean (SD) HDL-C	30.5 (7.60)	30.6 (6.70)	31.0 (8.14)	32.2 (9.47)
N	59	51	50	61
LSM, difference from Placebo (95% CI)		3.26 (-7.56, 14.12)	3.39 (-7.46, 14.29)	0.83 (-9.41, 11.06)
P-value		0.409 [r]	0.150 [r]	0.430 [r]
Lipid Variable LDL-C				
Baseline Mean (SD) LDL-C	91.4 (30.56)	94.2 (26.57)	95.0 (36.31)	100.0 (36.56)
N	59	51	50	61

	Placebo N=59	Epanova 2 g N=54	Epanova 3 g N=52	Epanova 4 g N=64
Baseline TG \leq750 mg/dL				
LSM, difference from Placebo (95% CI)		8.97 (-8.12, 26.19)	5.40 (-11.46, 22.38)	7.59 (-8.65, 23.82)
P-value		0.057 [r]	0.376 [r]	0.102 [r]
[1] Baseline = Average of Weeks -2, -1 and 0. [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12). [3] LSM differences from the ANCOVA model using natural log transformed data. [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. placebo. [r] indicates data were ranked prior to performing ANCOVA.				

Source: Applicant Jan 2014, SN0015.

Epanova was less efficacious at TG lowering in patients with baseline TG <750 mg/dL compared with those patients with a baseline TG \geq 750 mg/dL. Furthermore, the LSM difference from placebo analysis was not statistically significantly different for the Epanova 2g dose. Epanova was also less efficacious at lowering for non-HDL-C in patients with baseline TG <750 mg/dL.

Reviewer Comment: In the subgroup with baseline TG <750 mg/dL, the 2g Epanova dose was not statistically significantly different from placebo for TG, non-HDL-C, HDL-C or LDL-C. The 4g Epanova reduced TG and non-HDL-C to a lesser extent in this subgroup as compared to the overall mITT population. However, these are post-hoc analyses and therefore it is difficult to make any conclusive recommendations.

Analysis by Diabetes Status

The following table summarizes the results for the subgroup of patients in the mITT population by baseline diabetes status. Diabetes was defined as a history of diabetes, use of anti-diabetic medication, or HbA1c \geq 6.5%.

Table 30: Percent Change in Lipid Parameters from Baseline to End of Treatment in Diabetic Patients, mITT Population, EVOLVE study

	Placebo	Epanova 2 g	Epanova 3 g	Epanova 4 g
Lipid Variable TG				

	Placebo	Epanova 2 g	Epanova 3 g	Epanova 4 g
N	30	37	43	37
Baseline Median TG	666.7	749.3	733.7	639.3
Percent Change from Baseline				
N		35	43	35
LSM, difference from Placebo (95% CI)		-29.19 (-66.41, 6.11)	-19.16 (-56.94, 16.53)	-30.30 (-67.31, 4.74)
P-value		0.134 [r]	0.292 [r]	0.035 [r]
Lipid Variable Non-HDL-C				
N	30	37	43	37
Baseline Mean (SD) Non-HDL-C	209.1 (59.99)	204.9 (52.55)	224.8 (90.09)	212.5 (54.40)
Percent Change from Baseline				
N		35	43	35
LSM, difference from Placebo (95% CI)		-16.55 (-39.50, 5.95)	-9.70 (-32.45, 12.46)	-18.85 (-41.51, 3.31)
P-value		0.090 [r]	0.193 [r]	0.011[r]
Lipid Variable HDL-C				
N	30	37	43	37
Baseline Mean (SD) HDL-C	27.2 (9.21)	27.4 (6.42)	28.6 (7.59)	28.1 (6.61)
Percent Change from Baseline				

	Placebo	Epanova 2 g	Epanova 3 g	Epanova 4 g
N		35	43	35
LSM, difference from Placebo (95% CI)		0.53 (-16.84, 17.77)	-4.29 (-20.57, 11.72)	1.59 (-15.81, 18.88)
P-value		0.898 [r]	0.898 [r]	0.775 [r]

[1] Baseline = Average of Weeks -2, -1 and 0.
 [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).
 [3] LSM differences from the ANCOVA model using natural log transformed data.
 [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. placebo.
 [r] indicates data were ranked prior to performing ANCOVA.

Source: EVOLVE study report, Table 11.4.16, pg. 83.

Baseline median TG values for diabetics were similar to the overall mITT population, ranging from approximately 640 to 749 mg/dL across the four treatment groups. For TG lowering, relative to placebo, only the 4 g dose of Epanova showed a statistically significant percent difference from baseline (p=0.03).

Baseline mean non-HDL-C values for diabetics were similar to the overall mITT population, ranging from approximately 205 to 225 mg/dL across the four treatment groups. Relative to the placebo group, the LSM percent reduction of non-HDL-C among diabetics was -17%, -10% and -19%, respectively; however, only the 4 g Epanova dose group was significantly different than placebo.

Baseline mean HDL-C values for diabetics were similar to the overall mITT population, ranging from approximately 27 to 29 mg/dL across the four treatment groups. Relative to the placebo group, none of the LSM changes from baseline among the three Epanova groups were significant.

Reviewer Comment: In persons with diabetes, only the 4 g Epanova dose demonstrated statistically significant for changes in TG and non-HDL-C relative to placebo in percent change from baseline. However, the sample size was small and therefore generalizability is limited.

Analysis by Statin Use

The following table summarizes changes in lipid parameters of the subgroup of patients categorized according to their concomitant use of a statin.

Table 31: Baseline and Percent Change from Baseline to Endpoint in Lipid Parameters for Statin Users, mITT Population, EVOLVE study

	Placebo	Epanova 2 g	Epanova 3 g	Epanova 4 g
Lipid Variable TG				
N	33	35	34	36
Baseline Median TG	716.7	735.7	690.5	599.2
Percent Change from Baseline				
N		33	33	32
LSM, difference from Placebo (95% CI)		-32.02 (-73.00, 7.41)	-33.02 (-73.86, 6.25)	-32.73 (-73.94, 7.12)
P-value		0.096 [r]	0.045 [r]	0.037 [r]
Lipid Variable Non-HDL-C				
N	33	35	34	36
Baseline Mean (SD) Non-HDL-C	218.6 (60.91)	202.3 (53.32)	207.4 (69.84)	204.2 (64.30)
Percent Change from Baseline				
N		33	33	32
LSM, difference from Placebo (95% CI)		-18.69 (-42.91, 5.26)	-20.97 (-44.93, 2.68)	-17.85 (-42.33, 6.40)
P-value		0.028 [r]	0.010 [r]	0.025 [r]
Lipid Variable HDL-C				
N	33	35	34	36

	Placebo	Epanova 2 g	Epanova 3 g	Epanova 4 g
Baseline Mean (SD) HDL-C	31.0 (8.35)	29.3 (6.67)	29.4 (10.46)	28.0 (8.07)
Percent Change from Baseline				
N		33	33	32
LSM, difference from Placebo (95% CI)		8.51 (-6.66, 23.72)	4.58 (-10.31, 19.50)	10.85 (-4.62, 26.39)
P-value		0.028 [r]	0.057 [r]	0.033 [r]
[1] Baseline = Average of Weeks -2, -1 and 0. [2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12). [3] LSM differences from the ANCOVA model using natural log transformed data. [4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett's procedure for multiple comparisons of each Epanova vs. placebo. [r] indicates data were ranked prior to performing ANCOVA.				

Source: Study Report EVOLVE, Table 11.4.17, pg. 85.

As shown in the table above, relative to placebo, the 2 g, 3 g and 4 g Epanova groups showed LSM percent TG reductions of -32%, -33% and -33%, respectively; the differences from placebo were statistically significant for the 3 g and 4 g Epanova dose groups (ranked data) only.

For non-HDL-C, relative to placebo, the LSM percent reduction among statin users was markedly greater than in the overall mITT population: -19%, -21% and -18% in the 2g, 3g and 4 g Epanova dose groups, respectively, and all of which were significant on ranked data.

For HDL-C, relative to placebo, the LSM percent analyses of HDL-C among statin users also showed markedly greater increases than in the overall mITT population: 9%, 5% and 11% in the 2 g, 3 g and 4 g Epanova dose groups, respectively, that were significant on ranked data in the 2 g and 4 g Epanova dose groups.

Analysis by Age <65 or ≥ 65 years

The following table summarizes the results for the subgroup of patients in the mITT population by baseline age <65 years.

Table 32: Percent Change from Baseline to End of Treatment for TG, Subgroup Age <65 years, mITT Population, EVOLVE study

Age <65 years	Placebo N=87	Epanova 2 g N=91	Epanova 3 g N=93	Epanova 4 g N=83
Percent Change from Baseline to End of treatment	N=87	N=87	N=91	N=80
Mean (SD)	12.3 (79.00)	-19.8 (32.25)	-15.5 (66.97)	-23.8 (36.28)
Median	-8.4	-24.5	-23.8	-30.8
LS Mean, (95% CI)	-1.96 (-11.57, 8.69)	-25.00 (-32.34, -16.87)	-25.85 (-32.96, -17.98)	-30.33 (-37.39, -22.46)
LSM, difference from Placebo (95% CI)		-23.04 (-43.67, -2.75)	-23.89 (-44.26, -3.89)	-28.37 (-48.68, -8.37)
P-value		0.004[r]	0.002[r]	<0.001[r]

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons for TG and Hommel's procedure for Non-HDL-C and HDL-C comparing each Epanova vs. Placebo. [2] P-value from treatment effect from the above ANCOVA model comparing across all treatments.
 [r] Indicates the values were ranked prior to performing ANCOVA. *LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change+100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation
 Source: Epanova Study Report, Table 14.2.9.1.

Approximately 90% of the mITT population was <65 years of age. In this subgroup, relative to placebo, the LSM percent change from Baseline to End of Treatment for TG was similar to the overall mITT population.

The following table summarizes the results for the subgroup of patients in the mITT population by baseline age ≥65 years.

Table 33: Percent Change in TG from Baseline to End of Treatment, Subgroup ≥65 years, mITT Population, EVOLVE study

Age ≥65	Placebo N=11	Epanova 2 g N=8	Epanova 3 g N=4	Epanova 4 g N=16
Percent Change from	N=11	N=8	N=3	N=15

Age \geq 65	Placebo N=11	Epanova 2 g N=8	Epanova 3 g N=4	Epanova 4 g N=16
Baseline to End of treatment				
Mean (SD)	-12.8 (47.12)	-30.7 (34.21)	-15.4 (9.59)	-31.5 (24.77)
Median	-22.0	-32.7	-20.2	-30.3
LS Mean, (95% CI)	-8.1	-30.0	-22.7	-25.0
LSM, difference from Placebo (95% CI)		-21.9 (-53.11, 9.30)	-14.7 (-59.15, 29.85)	-16.9 (-43.66, 9.83)
Adjusted P-value		0.376	0.856	0.461

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons for TG and Hommel's procedure for Non-HDL-C and HDL-C comparing each Epanova vs. Placebo. [2] P-value from treatment effect from the above ANCOVA model comparing across all treatments. [r] Indicates the values were ranked prior to performing ANCOVA. *LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change+100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation

Source: Epanova Study Report, Table 14.2.9.1.

At baseline across the four treatment groups, there were only 39 (10%) patients with ages of \geq 65 years. The 2 g Epanova dose had a numerically greater reduction in the percent change from baseline to endpoint compared to the other two Epanova doses.

Analysis by Sex

The following table summarizes the results for the subgroup of patients in the mITT population by sex.

Table 34: Percent Change in TG from Baseline to End of Treatment, Subgroup Males, mITT Population, EVOLVE study

Males	Placebo N=76	Epanova 2 g N=79	Epanova 3 g N=75	Epanova 4 g N=71
Percent Change from Baseline to End of treatment	N=76	N=76	N=73	N=67

Males	Placebo N=76	Epanova 2 g N=79	Epanova 3 g N=75	Epanova 4 g N=71
Mean (SD)	16.8 (82.50)	-20.6 (31.22)	-14.6 (72.20)	-24.1 (35.65)
Median	-8.7	-25.2	-23.9	-30.7
LS Mean, (95% CI)	2.19 (-8.45, 14.07)	-25.40 (-33.17, -16.73)	-24.80 (-32.76, -15.90)	-30.43 (-38.08, -21.82)
LSM, difference from Placebo (95% CI)		-27.59 (-50.12, -5.49)	-26.99 (-49.75, -4.63)	-32.62 (-55.02, -10.60)
Adjusted P-value		0.001	<0.001	<0.001

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model.

P-values are adjusted using Dunnett's procedure for multiple comparisons for TG and Hommel's procedure for Non-HDL-C and HDL-C comparing each Epanova vs. Placebo. [2] P-value from treatment effect from the above ANCOVA model comparing across all treatments.

[r] Indicates the values were ranked prior to performing ANCOVA. *LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change+100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation

Source: Epanova Study Report, Table 14.2.9.1.

There were approximately 77% men in the overall mITT population. In the subgroup analysis by sex, Epanova was more efficacious at TG lowering in men compared to the overall mITT population---approximately 5-6% more TG reduction per Epanova dose.

The following table summarizes the results for women in the mITT population.

Table 35: Percent Change in TG from Baseline to End of Treatment, Subgroup Females, mITT Population, EVOLVE study

Females	Placebo N=22	Epanova 2 g N=20	Epanova 3 g N=22	Epanova 4 g N=28
Percent Change from Baseline to End of treatment	N=22	N=19	N=21	N=28
Mean (SD)	-15.8 (41.67)	-21.0 (37.58)	-18.6 (37.56)	-27.2 (32.91)
Median	-26.1	-23.2	-13.6	-30.6

Females	Placebo N=22	Epanova 2 g N=20	Epanova 3 g N=22	Epanova 4 g N=28
LS Mean, (95% CI)	-23.77 (-37.81, -6.58)	-28.61 (-42.60, -11.21)	-27.21 (-40.94, -10.30)	-31.56 (-42.94, -17.92)
LSM, difference from Placebo (95% CI)		-4.84 (-40.69, 31.34)	-3.44 (-39.01, 32.15)	-7.79 (-40.73, 23.97)
Adjusted P- value		0.984 [r]	0.991 [r]	0.726 [r]

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model. P-values are adjusted using Dunnett's procedure for multiple comparisons for TG and Hommel's procedure for Non-HDL-C and HDL-C comparing each Epanova vs. Placebo.
 [2] P-value from treatment effect from the above ANCOVA model comparing across all treatments.
 [r] Indicates the values were ranked prior to performing ANCOVA. *LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change+100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation

Source: EVOLVE study report, Table 14.2.9.1.

There were only 92 (23%) females in the study. The LSM difference from placebo in percent change in TG from baseline to endpoint was much smaller in women as compared to men. Women on olive oil (placebo) showed a median TG reduction that was better than the 2g or 3g Epanova treatment group.

Subgroup Analysis: Race

The following table summarizes the results for the subgroup of patients in the mITT population by race.

Table 36: Percent Change in TG from Baseline to End of Treatment, Subgroup Caucasian Race, mITT Population, EVOLVE study

Whites	Placebo N=94	Epanova 2 g N=92	Epanova 3 g N=88	Epanova 4 g N=88
Percent Change from Baseline to End of treatment	N=94	N=88	N=86	N=85
Mean (SD)	10.4 (77.53)	-20.9 (32.75)	-13.7 (68.16)	-27.2 (29.65)
Median	-10.4	-25.2	-22.4	-30.3
LS Mean, (95% CI)	-4.08 (-13.06, 5.83)	-26.66 (-33.70, -18.87)	-24.44 (-31.78, -16.31)	-32.00 (-38.69, -24.59)

Whites	Placebo N=94	Epanova 2 g N=92	Epanova 3 g N=88	Epanova 4 g N=88
LSM, difference from Placebo (95% CI)		-22.58 (-42.01, -3.39)	-20.36 (-40.12, -0.78)	-27.93 (-46.94, -9.17)
Adjusted P- value		0.004 [r]	0.017 [r]	< 0.001 [r]

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model.
 P-values are adjusted using Dunnett's procedure for multiple comparisons for TG and Hommel's procedure for Non-HDL-C and HDL-C comparing each Epanova vs. Placebo.
 [2] P-value from treatment effect from the above ANCOVA model comparing across all treatments.
 [r] Indicates the values were ranked prior to performing ANCOVA. *LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change+100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation

Source: EVOLVE study report, Table 14.2.9.1.

Approximately 92% of the mITT population was White/Caucasian. As summarized in the table above, relative to placebo, the percent change in TG from Baseline to End of Treatment in Caucasians was comparable to the overall mITT population.

The following table summarizes the results for the subgroup of patients in the mITT population by non-whites.

Table 37: Percent Change in TG from Baseline to End of Treatment, Subgroup Non-White Race. mITT Population, EVOLVE study

Non-Whites	Placebo N=4	Epanova 2 g N=7	Epanova 3 g N=9	Epanova 4 g N=11
Percent Change from Baseline to End of treatment	N=4	N=7	N=8	N=10
Mean (SD)	-12.0 (36.88)	-18.1 (29.32)	-34.7 (28.52)	-6.7 (63.04)
Median	-19.0	-23.0	-36.4	-35.3
LS Mean, (95% CI)	-7.39 (-47.00, 61.82)	-4.54 (-42.48, 58.43)	-25.96 (-54.52, 20.54)	-19.51 (-42.95, 13.57)
LSM, difference from Placebo (95% CI)		2.85 (-123.78, 123.23)	-18.57 (-134.76, 81.76)	-12.12 (-122.84, 71.46)

Non-Whites	Placebo N=4	Epanova 2 g N=7	Epanova 3 g N=9	Epanova 4 g N=11
Adjusted P-value		0.997 [r]	0.728 [r]	0.817 [r]

[1] Adjusted P-value from treatment effect from an ANCOVA model that includes terms for treatment, baseline value as a covariate, along with a stratification factor for users and non-users of permitted lipid-altering drugs (statin, CAI or their combination) as a covariate in the model.

P-values are adjusted using Dunnett's procedure for multiple comparisons for TG and Hommel's procedure for Non-HDL-C and HDL-C comparing each Epanova vs. Placebo.

[2] P-value from treatment effect from the above ANCOVA model comparing across all treatments.

[r] Indicates the values were ranked prior to performing ANCOVA. *LS means and LS mean differences from the above ANCOVA model using natural log transformed percent change as log of (percent change+100). LS means, LS mean differences and 95% CIs were back-transformed for tabulation

Source: EVOLVE study report, Table 14.2.9.1.

There were only 31 non-white patients in the study. The results for the percent change in TG relative to placebo were not significant.

Reviewer Comment: For the subgroups of patients <65 years of age, men, and White, the TG treatment effect was similar to the overall population. However, likely due to the small sample size, in the subgroup of patients \geq 65 years of age, women, and non-White, the TG treatment effect was numerically different from the overall population.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

On March 5, 2014, DMEP requested the applicant to provide justification and clinical data to support daily dosing of 2g and 4g Epanova as proposed in the applicant's draft labeling. This request was based on observation that dose-dependent increases in circulating levels of EPA and DHA were not clearly paralleled by dose-dependent reductions in TG. Despite large increases in plasma EPA from the 2 g to 4 g dose (267% to 406%) the difference in TG lowering was modest between the two doses (point estimate of -26% to -31% with overlapping CIs). The three different doses of Epanova elicited decreases in TG that were not distinguishable from each other, albeit each dose was statistically significantly better than placebo.

The applicant responded on March 14, 2014 that with the unique pharmacology of Epanova, the TG lowering dose-response between the 2 g and 4 g regimens had an apparent curvilinearity, i.e., incremental lipid lowering that was not dose-proportional but dose-dependent. This curvilinear dose-response is also observed with statins, i.e. doubling the dose leads to a disproportionate incremental benefit (6% reduction). Therefore, the applicant proposed the benefit-risk with both Epanova dosages will offer a significant clinical option (b) (4) at 2 g or 4 g/day, (b) (4)

(b) (4) as needed to effectively treat patients with severe hypertriglyceridemia.

The applicant continued that the TG reductions with the 2g and 4g doses were associated with mean decreases in TG levels of approximately 181 and 219 mg/dL, respectively. Furthermore, the safety analyses in the EVOLVE study demonstrated a favorable safety profile for the 2 and 4 g dosing with Epanova that was consistent with previously reported trials of omega-3 interventions. As shown in the following table, there were no apparent differences among the Epanova dosing groups in the patterns of occurrence for overall AEs, and while related adverse events (mostly gastrointestinal) were reported more frequently with 4 g than 2 g Epanova, most were considered mild or moderate in severity.

Table 38: Summary of TG Lowering and Adverse Events with 2g and 4g Epanova, EVOLVE Study

Triglycerides (TG)	Olive Oil (N=99)	EPANOVA	
		2 g (N=100)	4 g (N=99)
Baseline, mg/dL [1]			
N	98	99	99
Mean (SD)	788.5 (305.11)	790.1 (269.01)	783.6 (335.21)
Median	682.3	717.0	655.0
Change at End of Treatment, mg/dL [2]			
N	98	95	95
Mean (SD)	91.5 (700.07)	-180.7 (286.99)	-218.8 (350.17)
Median	-71.3	-170.7	-178.0
% Change at End of Treatment [2]			
N	98	95	95
Mean (SD)	9.5 (76.32)	-20.7 (32.37)	-25.0 (34.72)
Median	-10.4	-24.5	-30.7
LSM [3]	-4.26	-25.94	-30.86
P-Value [4]		0.005 [r]	< 0.001 [r]
Subjects with TG <500 mg/dL at End of Treatment (Week 12)	(N=98)	(N=95)	(N=95)
Yes, n (%)	36 (36.7)	37 (38.9)	49 (51.6)
No, n (%)	62 (63.3)	58 (61.1)	46 (48.4)
Adverse Events [5]	(N=99)	(N=100)	(N=99)
Subject With Any AE, n (%)	26 (26.3%)	40 (40.0%)	44 (44.4%)
Serious, n (%)	2 (2.0%)	1 (1.0%)	0 (0.0%)
Severe, n (%)	5 (5.1%)	2 (2.0%)	1 (1.0%)
Related to IP, n (%) [6]	3 (3.0%)	18 (18.0%)	25 (25.3%)
Caused Discontinuation, n (%)	0 (0.0%)	5 (5.0%)	5 (5.1%)
[1] Baseline = Average of Weeks -2, -1 and 0.			
[2] % Change from Baseline to End of Treatment (Average of Weeks 10 and 12).			
[3] LSM from the ANCOVA model using natural log transformed data.			
[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a			

Triglycerides (TG)	Olive Oil (N=99)	EPANOVA	
		2 g (N=100)	4 g (N=99)
covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values for TG comparisons were adjusted using Dunnett's procedure for multiple comparisons of each EPANOVA vs. olive oil.			
[5] If a subject experiences the same event more than once, or more than one event, only the occurrence with the highest degree of categorical relevance is tabulated.			
[6] Related means possibly, probably, or definitely related.			
[r] Indicates data were ranked prior to performing ANCOVA.			
Source: EVOLVE Tables 14.2.1.1, 14.2.7.1 and 14.3.1.1.			

Source: Applicant Response, March 14, 2014.

The applicant conducted an *ad hoc* analysis of the number and proportion of patients with TG-lowering categorized by percent reduction at end of treatment. According to the applicant, dose-dependent increases in the number of patients achieving greater TG reductions in the 4 g versus the 2 g Epanova regimen became apparent for >30% and >40% TG reductions. At the lowest category of TG reductions (10% or less), both the placebo and the 2 g dose groups had the largest number of patients. Therefore, according to the applicant, the 4 g Epanova dose was apparently more effective than the 2 g dose across the range of baseline TG levels.

Table 39: Number and Proportion of Patients with TG-Lowering Categorized by Percent Reduction at End of Treatment (Week 12), EVOLVE study

Statistics	Olive Oil (N=98)	Epanova 2g (N=99)	Epanova 4g (N=99)	p-value[1]
Percentage Reduction at End of Treatment, n (%)				<0.001
>40%	16 (16.3)	24 (25.3)	29 (30.5)	
>30 to <=40%	12 (12.2)	18 (18.9)	21 (22.1)	
>20 to <=30%	10 (10.2)	13 (13.7)	14 (14.7)	
>10 to <=20%	11 (11.2)	10 (10.5)	9 (9.5)	
<=10%	49 (50.0)	30 (31.6)	22 (23.2)	
P-value for Pairwise Comparison [1]				
Epanova vs Olive Oil		0.008	<0.001	
Epanova 4 g vs Epanova 2 g			0.170	

Note: Percentage is based on subjects with non-missing value at end of treatment.
 [1] p-value is obtained from Cochran-Mantel-Haenszel Chi-Square test based on row mean scores.

Source: Applicant Response, March 14, 2014

I considered the applicant's justification to support both the 2 and 4g doses of Epanova. On the basis that there may be a small number of patients who respond to a slightly greater extent to the 4g than the 2g dose, I recommend that both doses be approved to afford physicians more flexibility to individualize therapy. However, the hard clinical

outcome (pancreatitis) of providing a 5% (and an absolute difference of 7 mg/dL) greater TG reduction with the 4g over the 2g dose is unknown.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The EVOLVE and ESPRIT trials evaluated efficacy over 12 weeks and 6 weeks respectively and therefore did not assess persistence of efficacy for longer periods. However, the EPIC-1 and EPIC-2 trials, which evaluated Epanova in the maintenance of remission of Crohn's disease, were conducted up to 58 weeks. These trials were reviewed for safety, but the laboratory data included plasma levels of TG measured at Baseline, Week 30 and Week 52 for EPIC-1 and plasma TG levels at Baseline, Week 30 and Week 58 for EPIC-2.

The TG values from EPIC-1 and EPIC-2 demonstrated that 4 g/day of Epanova decreased TG by 15% and 19%, respectively. The corresponding TG changes in patients who received placebo were +11% in EPIC-1 and -4% in EPIC-2. Therefore, a persistence of effect with Epanova was demonstrated for 52 weeks in EPIC-1 and 58 weeks for EPIC-2 in Crohn's disease patients.

6.1.10 Additional Efficacy Issues/Analyses

As described in the previous section, Epanova 3g per day showed unpredictability in response. In order to explore the unpredictability/ variability observed in the Epanova 3 g/day group, the applicant conducted post-hoc analyses. The applicant defined patients with a greater than 800% increase in EPA but less than 5% TG lowering response as having a presumed lipoprotein lipase impairment and designated these patients as "Functional Type 1" patients.

This reviewer emailed the applicant with the following question:

"Explain the justification for the greater than 800% increase in EPA, but less than 5% decrease in TG used to define the 26 patients with this syndrome in the EVOLVE trial. How do you presume these patients are similar to patients with lipoprotein lipase (LPL) impairment?"

On November 2103, the applicant responded they selected a "threshold of 800 percent change in plasma EPA (the predominant omega-3 in Epanova), which is about two-fold higher than the LS mean change of EPA in the highest dose group (4 grams). EPA was chosen rather than EPA+DHA because the baseline levels of EPA are much lower than DHA and it has a much shorter half-life and thereby the change in EPA levels is a more sensitive marker of Epanova's acute intake."

The applicant further proposed that “since measurements of omega-3 plasma levels are readily available, the proposed definition of LPL impairment (>800% increase in EPA with < 5% reduction in plasma TG’s) can be utilized by clinicians to identify a mechanism by which a patient does not respond to Epanova and thereby requires a change in therapeutic approaches [such as] severe fat restriction and/or insulin therapy.”

Although the approach taken by the applicant is intriguing, another explanation of the dose response is that 3 g of Epanova is spaced too closely to 2g to demonstrate reliable differences between the two doses.

7 Conclusions on Efficacy Review

From an efficacy reviewer perspective, I am recommending that Epanova be approved for the indication as an adjunct to diet to reduce TG in adults with severe pancreatitis. The dosage of Epanova is 2 grams or 4 grams daily and physicians should be instructed to individualize therapy according to patient response and tolerability.

In the pivotal Phase 3 trial, treatment with Epanova led to statistically significant reductions in fasting TG levels with median differences in percent change of -16% (95% CI, -26% to -6%) for Epanova 2g per day and -21% (95% CI, -31% to -11%) for Epanova 4g per day relative to placebo. Although treatment with Epanova resulted in statistically significant reductions in non-HDL-C levels compared with placebo, it increased levels of LDL-C as well. The changes in lipid parameters are summarized in the following table.

Table 40: Median Baseline and Median Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia

Parameter (mg/dL)	EPANOVA 2 g N = 100		EPANOVA 4 g N = 99		Placebo ^a N = 99		EPANOVA 2 g vs. Placebo	EPANOVA 4 g vs. Placebo
	BL	% Change	BL	% Change	BL	% Change	Treatment Difference in % change ^b	
TG	717	-25	655	-31	682	-10	-16 **	-21 ***
Non-HDL-C	205	-8	225	-8	215	-1	-7 *	-10 **
HDL-C	27	+7	29	+5	29	+2	+5 †	+4 †
TC	241	-6	254	-6	246	0	-6	-9
VLDL-C	123	-25	126	-35	125	-11	-14	-21
LDL-C	77	+21	90	+26	78	+10	+13	+15
Apo B	114	+6	118	+6	110	+2	+3	+2

^a Placebo = Olive Oil
^b Difference = Median of [EPANOVA % Change – Placebo % Change] (Hodges-Lehmann Estimate)
 † not significant; * for p < 0.05; ** for p < 0.01; *** for p < 0.001
 Testing for statistical significance, with multiplicity adjustment where appropriate, was performed for TG, non-HDL-C, and HDL-C. P values were obtained from an ANCOVA model using rank-transformed data that included terms for treatment and use of lipid-altering drugs as factors and the baseline value as a covariate. Testing for statistical significance was not performed for TC, VLDL-C, LDL-C, or Apo B.

Labeling should qualify that the effects of Epanova on the risks for pancreatitis and cardiovascular mortality and morbidity have not been determined.

8 Appendix

Clinical Investigator Financial Disclosure Review Form

Application Number: 205060

Submission Date(s): July 5, 2013

Applicant: Omthera Pharmaceuticals

Product: Epanova (omega-3-carboxylic acids)

Reviewer: Iffat Nasrin Chowdhury, MD

Date of Review: March 3, 2014

Covered Clinical Study (Name and/or Number): Study OM-EPA-003 (EVOLVE)

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>74 in the EVOLVE study</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): N/A Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		

Is an attachment provided with the reason: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)
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Reviewer Comment:

As stated in the body of the review, a signed FDA form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was included in the submission declaring the absence of financial interests and arrangements between the applicant and clinical investigators. The form was appended with a list of investigators who participated in all the Phase 2 and Phase 3 studies. There were no investigators who were also sponsor employees. Furthermore, the pivotal trial was a randomized, double-blind design with lipid parameters as objective endpoints; therefore the integrity of the data is not called into question. The approvability of the application is not affected by financial interests/arrangements.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IFFAT N CHOWDHURY
05/02/2014

JAMES P SMITH
05/03/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205060
Priority or Standard	Standard
Submit Date(s)	July 5, 2013
Received Date(s)	July 5, 2013
PDUFA Goal Date	May 5, 2014
Division / Office	Division of Metabolism and Endocrinology Products/ Office of New Drugs
Reviewer Name(s)	Giovanni Cizza, MD, PhD, MHSc
Review Completion Date	March 22, 2014
Established Name	Omega-3-carboxylic acids
(Proposed) Trade Name	Epanova
Therapeutic Class	Lipid-lowering Agent
Applicant	Omthera Pharmaceuticals
Formulation(s)	1 gram capsules
Dosing Regimen	2 grams or 4 grams daily (proposed)
Indication(s)	Severe hypertriglyceridemia
Intended Population(s)	Patients with TG \geq 500 mg/dL

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1 Recommendations/Risk Benefit Assessment

This document contains the clinical safety review for Epanova, NDA 205060. General background materials pertaining to this application, along with the review of clinical efficacy, are addressed in a separate review conducted by Dr. Iffat Chowdhury.

1.1 Recommendation on Regulatory Action

The applicant, Omthera Pharmaceuticals, Inc., submitted a 505(b)(1) new drug application for Epanova (omega-3-carboxylic acids) which they propose for use as an adjunct to diet to reduce triglycerides (TG) levels in adult patients with severe hypertriglyceridemia (defined as TG \geq 500 mg/dL). This clinical reviewer recommends approval of the 2g and 4g doses of Epanova on the basis of the data submitted in support of the safety, tolerability and efficacy of this product. For specific comments on the efficacy refer to Dr. Iffat Chowdhury's review.

In the only pivotal trial (EVOLVE; described in Section 5), Epanova was administered in doses of 2g, 3g, and 4g per day. However, the applicant is seeking approval of only the 2g and 4g doses. Had the applicant sought approval for the 3g dose, this reviewer would not have recommended approval of that dose for the proposed indication. As highlighted in this review, the 3g dose appeared to be less well tolerated than the 4g dose, while not conferring better efficacy.

1.2 Risk Benefit Assessment

This review focuses on clinical safety alone and does not address efficacy. The efficacy of Epanova is addressed in Dr. Iffat Chowdhury's clinical review. Validity of the safety data is supported by the applicant's risk evaluation process, including detailed, pre-planned study procedures that were followed in their single, controlled Phase III trial. The data analysis plan was pre-specified, and the data were collected prospectively. Although the patient retention rate in the main trial was high, the trial was only 12 weeks in duration. In summary, in consideration of the clinical benefits reported in Dr. Chowdhury's efficacy review, the overall tolerability and risk/benefit balance favor approval of the 2 g and 4g doses of Epanova as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable

2 Introduction and Regulatory Background

Epanova is an omega-3 free fatty acid (FFA) preparation of which approximately (b) (4) % is composed of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

On March 25, 2010, IND 107616 was submitted, and included an End-of-Phase 2 (EOP2) meeting request to discuss the applicant's plan to develop this compound as an adjunct to diet for the treatment of severe hypertriglyceridemia (>500 mg/dL). Epanova had been previously investigated in the Division of Gastrointestinal and Inborn Errors Products for the treatment of Crohn's Disease (IND (b) (4)) (EPIC studies). The sponsor of that application was Tillots Pharma AG, and ownership of the application was transferred to Omthera on December 8, 2009.



During drug development, the following protocols were reviewed under Special Protocol Assessments:

1. OM-EPA-003 (later called EVOLVE): *Efficacy and Safety of Epanova® in Severe Hypertriglyceridemia.*
2. OM-EPA-004 (later called ESPRIT): *A 6-Week, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Add-on Epanova to Statin Therapy in High-Risk Subjects with Persistent Hypertriglyceridemia.*
3. OM-EPA-005 (STRENGTH): *A Phase III, Double-Blind, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia.*

On April 25, 2012, the applicant requested agency concurrence on the proposal, in lieu of conducting a thorough QTc study, assess ECGs recorded pre-dose and during

periods of trough levels after dosing with dosing with Epanova for multiple days in the EVOLVE study. This proposal was found acceptable on October 3, 2012.

On November 14, 2012 a pre-NDA meeting was held. During the discussion, it was agreed that:

- The proposed content of the clinical package was adequate for submission of the NDA
- The proposed studies provided adequate safety database of reasonable size and duration.

3 Ethics and Good Clinical Practices

Overall, the data submitted in this NDA were of sufficient quality and completeness to permit a substantive review of safety. The applicant provided listings of recorded protocol deviations. In EVOLVE, the pivotal trial, study 003, there were a total of 10 subjects who were randomized and violated the exclusion criteria: 9 of the 10 violations were for uncontrolled diabetes, one was for a subject with a history of chronic pancreatitis. The subjects with abnormal glucose were retested at the next visit and, based on normalized values, were allowed to continue in the trial. The subject with previous history of chronic pancreatitis was allowed to continue because the investigator considered the recovery time prior to randomization sufficient. In ESPRIT there was only one protocol violation. No irregularities were identified, and the few reported protocol violations detected would not be expected to appreciably influence the overall safety findings. The applicant states that the trials addressed in this application were in accordance with US Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Please refer to Dr. Iffat Chowdhury's clinical efficacy review for details pertaining to Section 3, including financial disclosures. Additional information pertaining to the sources of safety data are addressed in Section 5 of this review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

The primary reviews pertaining to CMC, clinical microbiology, preclinical pharmacology/toxicology, and clinical pharmacology have been completed. However, no significant safety issues pertaining to these disciplines have been raised. Please refer to Iffat Chowdhury's clinical efficacy review for additional details pertaining to Section 4.

5 Sources of Clinical Data

Refer to Dr. Iffat Chowdhury's clinical review of efficacy for additional information regarding the sources of clinical data and for detailed descriptions of the individual clinical studies conducted in support of the safety and effectiveness of Epanova.

In this new drug application, the applicant submitted data from ten clinical studies to support the safety and efficacy of Epanova for improving triglyceride levels in patients with severe hypertriglyceridemia. Five clinical studies were conducted by Omthera Pharmaceuticals in patients with severe hypertriglyceridemia. Five additional clinical studies, characterized by the applicant as supportive, were conducted by Tillots Pharma AG in patients with Crohn's disease. The applicant is relying on the therapeutic trials conducted by Omthera as the primary source of data to serve as the foundation for scientific evidence in support of safety and efficacy. The five trials from Omthera included a Phase II PK/BA study, a Phase I PK/PD/BA study to determine the effects of multiple doses of Epanova on the PK and anti-coagulant activity of a single dose of warfarin, a Phase I PK/BA study to determine the effects of multiple doses of Epanova on simvastatin, and two Phase III studies to determine the safety and efficacy of Epanova in patients with hypertriglyceridemia. The two Phase III studies, EVOLVE, study 003 and ESPRIT, study 004 were similar in design. They were randomized, olive oil-controlled, parallel group studies. Study duration however differed: study 003 had 12 week duration, study 004 had 6 week duration.

5.1 Tables of Studies/Clinical Trials

A tabulation and detailed description of all completed clinical studies in the Epanova development program is provided in Section 5 of Dr. Iffat Chowdhury's clinical efficacy review. These are not reproduced in this review in order to minimize duplication.

Key issues of relevance to the understanding and interpretation of safety findings such as study objectives, design, study inclusion and exclusion criteria, formulations, dosing and administration, comparators, and concomitant medications are addressed in

Section 7 of this review. Table 1 provides a summary of all clinical trials conducted with Epanova by Omthera as of July 2013.

For the safety analyses, the Sponsor grouped studies in the following three pools:

- Pool A (Phase III Pivotal Study, EVOLVE, Study OM-EPA-003 and the other Phase III Study, OM-EPA-004)
- Pool B (EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)
- Pool C (long-term [≥52 weeks] safety data from EPIC-1, EPIC-2, EPIC-3, and EPIC-1E).

Pool A included subjects with hypertriglyceridemia; Pool B and C included subjects with Crohn’s disease, Pool B and C differed because Pool C comprised the long-term exposure studies which were an extension of the studies in Pool B.

Table 1: Listing of Clinical Studies Conducted by Omthera in Healthy Subjects and in Subjects with Hypertriglyceridemia

Study	Dose/duration	No. of Subjects	Key inclusion Criteria
OM-EPA-001: A Phase II, PK/BA, randomized, open-label, 4-way crossover study, with 4 single-dose treatment periods and a 7-day washout in between each treatment to compare the bioavailability of EPA and DHA, assessed by measurements of the AUC in plasma, after fasting and a high-fat meal, from a single 4g dose of Epanova and Lovaza	Epanova 4g x2 (a.m. fasted and high fat meal) Lovaza 4g x2 (a.m. fasted and high fat meal) 2 single dose of each of Epanova and Lovaza	54	Healthy Men or Women, age ≥18 years
OM-EPA-006: A Phase I, PK/PD/BA, open-label, 2-cohort (Cohort 1: Treatment A: Single dose of warfarin w/o Epanova; Treatment B: single dose of warfarin with 4g QD Epanova; Cohort 2: Treatment C: 4g QD of Lovaza following low fat breakfast), parallel design study to determine the effects of multiple doses of Epanova on pharmacokinetic and anti-coagulant activity of single dose warfarin and to compare the systemic exposure of total EPA, total DHA, and total EPA+DHA following multiple-dose administration of Epanova compared to multiple-dose administration of Lovaza	Epanova 4g Lovaza 4g Cohort 1: 21 days Cohort 2: 14 days	52 (Epanova, N=26) (Lovaza N=26)	Healthy Men or Women, age 18-55 years

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Study	Dose/duration	No. of Subjects	Key inclusion Criteria
(omega-3 acid ethyl esters)			
OM-EPA-007: A Phase I, PK/BA, open-label, 2-way crossover study with 2 week washout between treatments; no comparator to determine effect of multiple doses of Epanova on multiple-dose PK of simvastatin	Treatment A: 40mg simvastatin; 81 mg of aspirin, and 4g of Epanova Treatment B: 40mg simvastatin; 81 mg of aspirin Treatment A: 14 days Treatment B: 14 days	52	Healthy Men or Women, age 18-55 years
OM-EPA-003: A Phase III, Efficacy PK/PD, randomized, double-blind, olive-oil controlled, parallel group design to evaluate the efficacy and safety of Epanova in subjects with severe hypertriglyceridemia	Epanova 2g QD arm (n=100) Epanova 3g QD arm (n=101) Epanova 4g QD arm (n=99) Olive oil (placebo) QD arm (n=99) 12 weeks	399	Men or Women, age ≥ 18 years with serum TG values at screening in the range ≥ 500 mg/dL and < 2000 mg/dL
OM-EPA-004: A Phase III, Efficacy PK/PD, randomized, double-blind, olive-oil controlled, parallel group design to evaluate the efficacy and safety of adding Epanova to statin therapy for lowering non-HDL cholesterol in subjects with persistent hypertriglyceridemia and high-risk for cardiovascular disease	Epanova 2g QD arm (n=215) Epanova 4g QD arm (n=216) Olive oil (placebo) QD arm (n=216) 6 weeks	647	Men or Women, age ≥ 18 years At high risk for a future cardiovascular event (with high serum TG ≥ 200 and < 500 mg/dL despite being on a statin for at least 4 weeks prior to screening
List of Abbreviations: AUC = Area under the Curve BA = Bioavailability DHA = Docosahexaenoic Acid EPA = Eicosapentaenoic Acid Non-HDL = Non-High-Density Lipoprotein PD = Pharmacodynamics PK= Pharmacokinetic QD= Every Day TG = Triglyceride			

Source: created by the reviewer from Tabular listing of all clinical studies, Table 5.2-1, pages 2-4.

Table 2 provides a summary of supportive clinical trials sponsored by Tillots Pharma AG and conducted with Epanova as of July 2013

Table 2: Listing of Supportive Clinical Studies

Study	Dose/duration	No. of Subjects	Key inclusion Criteria
<p>SPC-275-4: A Phase I, randomized, placebo and active controlled, multiple dose study to evaluate the safety and PK of multiple increasing oral doses of Epanova</p>	<p>Epanova (b) (4) 2g/d (b) (4) 4g/d (b) (4) 8g/d (b) (4) 4.5 g/d (b) (4) (2g QD+ 2.5g QD) MaxEpa (fish oil) 9g/d (4g QD+ 5g QD) Placebo (triglyceride saturated fatty acids) 8g/d (4g BID) 42 days (6 weeks)</p>	<p>73</p>	<p>Healthy Men or Women, age 18-60 years</p>
<p>TP0307 (EPIC-1): A Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel-group study to assess the ability of Epanova Soft Gelatin Capsules taken at a total daily dose of 4g to maintain remission in Crohn's Disease patients in whom remission, stable for at least 3 months and no longer than 1 year, had been induced by corticosteroids, azathioprine/6-MP, methotrexate, 5-ASA or antibiotics.</p>	<p>Epanova: Week 1: 1g; Week 2: 2g (b) (4), Week 3 to Week 52: 4g (b) (4) (n=188) Placebo (TG): Week 1: 1g; Week 2: 2g (b) (4), Week 3 to Week 52: 4g (b) (4) (n=186) 52 weeks</p>	<p>383*</p>	<p>Subjects in remission from CD 3-12 months (CDAI < 120) and off steroids and immunosuppressants</p>
<p>TP0308 (EPIC-2): A Phase III, multi-center, randomized, double-blind, placebo-controlled, parallel-group</p>	<p>Epanova: 1g for 7 days; 2g (b) (4) days 8-14;</p>	<p>379</p>	<p>Subjects with active CD who respond to induction therapy and are in remission prior to</p>

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multicenter study to assess the efficacy and safety of Epanova for the maintenance of symptomatic remission in subjects with CD who are responding to steroid induction therapy	4g (b) (4) daily thereafter (n=189) Placebo (TG) Same regimen (n=190)		study therapy
TP0309 (EPIC-3): A Phase IIb, two-center open-label, no comparator study to assess the PK/PD safety and tolerability of Epanova in CD patients in remission	Epanova 4g (b) (4) 52 weeks	25	Subjects in remission from CD 3-24 months (CDAI < 150 and off steroids/immunosuppressants)
TP0307 (EPIC-1E): A Phase III, multi-center, open-label, extension study, all subjects received Epanova to assess the long-term safety and tolerability profile of Epanova in patients with CD	1g x 7 days, then 2g (b) (4) on days 8-14 and to 4g (b) (4) 36 months	82	Subjects enrolled to EPIC-1, EPIC-2, or EPIC-3 regardless of treatment received in those studies
BA = Bioavailability CD = Crohn's disease CHD = Coronary Heart Disease NCEP = National Cholesterol Education Program PD = Pharmacodynamic PK – Pharmacokinetic TLC = Therapeutic Lifestyles Changes * "Of the 383 subjects originally randomized, 9 randomized subjects were excluded by the Sponsor from Site 72 because the site had not met regulatory requirements" ref page 13 Abbreviated CSR Study TP0307			

Source: created by the reviewer from Tabular listing of all clinical studies, Table 5.2-2, pages 2-4.

The Sponsor categorized the ten studies submitted in three different sets:

- a) Clinical pharmacology/pharmacokinetic, conducted in healthy subjects (Healthy Subjects Dataset).
- b) Phase III studies, conducted in subjects with hypertriglyceridemia defined in Study OM-EPA-003 (EVOLVE) as baseline TG level between ≥ 500 mg/dL and < 2000 mg/dL, and in Study OM-EPA-004 (ESPRIT) as baseline TG level ≥ 200 mg/dL and < 500 mg/dL and high risk for cardiovascular disease (Hypertriglyceridemic Placebo-Controlled Dataset).
- c) Studies in subjects with Crohn's disease (Crohn's Dataset).

The Healthy Subjects Dataset included four studies: two clinical pharmacology/pharmacokinetic (PK) studies and two drug-drug interaction (DDI) studies. Of these four studies, two were controlled and two uncontrolled, The PK studies included a phase I dose-escalation study (SPC 275-4) and a study that compared the bioavailability of a single dose of Epanova to Lovaza® in healthy subjects (OM-EPA-001).

The two DDI studies included one study with warfarin (OM-EPA-006) and another study with simvastatin (OM-EPA-007). These studies involved a total of 180 healthy subjects exposed to various doses of EPANOVA ranging from 2 to 8g/day and 157 healthy subjects exposed to various controls, including placebo, olive oil, saturated fatty acids, simvastatin, and acetylsalicylic acid.

The Hypertriglyceridemic Placebo-Controlled Dataset included two Phase III trials EVOLVE and ESPRIT. EVOLVE was designed to support the primary indication for the treatment of severe hypertriglyceridemia, had a duration of 12 weeks, and included 99 subjects on placebo (olive oil) and 300 subjects on EPANOVA 2g, 3g, or 4g/day. ESPRIT was designed to investigate EPANOVA as an adjunct to diet and statin therapy in high-risk subjects who have persistent hypertriglyceridemia (fasting TG levels ≥ 200 and <500 mg/dL) despite being on diet and statin therapy. ESPRIT had a shorter duration, six weeks, and involved 215 subjects on placebo (olive oil), and 431 subjects on EPANOVA 2g or 4 g/day.

The Crohn's Disease Dataset included a total of four studies all sponsored by Tillots. They included two placebo ((Miglyol® 812)-controlled Phase III studies, EPIC-1 (TP0307) and EPIC-2 (TP0308), one Phase IIb pharmacokinetic/ pharmacodynamic (PK/PD) study (Study TP0309 [EPIC-3]), and one open-label extension to these three studies (Study TP0307 open-label extension [EPIC-1E]).

The Overall Integrated Dataset included safety information obtained from all subjects exposed to any dose of EPANOVA in the Hypertriglyceridemic Placebo-Controlled dataset and the double-blind phases of the Crohn's Placebo-Controlled.

Reviewer's note: Reported below are some general comments on the overall duration of exposure and doses used as they relate to the safety and tolerability of Epanova. The study duration of the two Phase III studies conducted in subjects with hypertriglyceridemia was relatively short in light of the chronic use that this class of drugs is destined to, but still acceptable based on the collective knowledge available on this class of drugs. The Phase III pivotal trial for severe hypertriglyceridemia, Study 003, lasted 12 weeks and the other Phase III trial, study 004 lasted only 6 weeks. The database submitted by the applicant did include other controlled studies, namely EPIC-1 and EPIC-2 which had a longer duration, approximately one year, and were conducted in subjects with Crohn's disease. These supportive studies were useful in providing long-term information on the use of the drug with the following limitation: patients Crohn's disease often suffer from gastrointestinal symptoms and Epanova is associated with gastrointestinal symptoms.

Finally, as described in greater detail in this document, there were several instances in which EPANOVA 3g appeared less well tolerated than 4g. The Sponsor did not seek approval for Epanova 3g; since this dose was nevertheless tested in EVOLVE, the pivotal trial, this finding should be mentioned. For specific comments on the efficacy of Epanova 3g, refer to the review of clinical efficacy, authored by Dr. Iffat Chowdhury.

5.2 Review Strategy

The evaluation of safety considered all Epanova clinical studies with particular emphasis on Pool A.

5.3 Discussion of Individual Studies/Clinical Trials

Refer to Section 5.3 of Dr. Iffat Chowdhury's clinical review for a discussion of the individual studies that contributed to the evaluation of efficacy. In addition to the two studies conducted in subjects with hypertriglyceridemia, in support of the safety and tolerability the Sponsor submitted a series of studies conducted in subjects with Crohn's disease. These studies are briefly described below.

EPIC-1 had duration of 52 weeks, included 374 analyzed subjects with Crohn's disease (out of 383 subjects originally randomized): 186 analyzed subjects with Crohn's disease exposed to placebo and 188 analyzed subjects with Crohn's disease exposed to Epanova 4g/day. The primary endpoint was maintenance of remission in subjects with Crohn's disease in whom remission had been induced by corticosteroids, azathioprine/6-MP, methotrexate, 5-ASA or antibiotics. Laboratory safety evaluations included hematology, serum chemistry, serum lipids, and urinalysis and serum pregnancy and were performed three times in the course of the study (Visit 1, Week-1; Visit 9, Week 30; and Visit 14; Week 52).

EPIC-2 had duration of 58 weeks, included a total of 379 randomized subjects with Crohn's disease: 190 subjects with Crohn's disease randomized to placebo and 189 subjects with Crohn's disease randomized to Epanova 4g/day. EPIC-1 and EPIC-2 were designed to investigate the previous Sponsor's interest in the maintenance of remission in Crohn's disease. Subjects were either in remission from their disease or stabilized on a lead-in regimen (EPIC-2). The primary endpoint was time to relapse of disease. Laboratory safety evaluations included hematology, serum chemistry, serum lipids, urinalysis and serum and urine pregnancy and were performed at the following visits: Visit 1 (Screening Week - 8), Visit 3 (Week 0), Visit 5 (Week 8), Visit 7 (Week 16), Visit 10 (Week 30), Visit 13 (Week 44), and Visit 16 (Week 58).

EPIC-3 (TP0309) had duration of 52 weeks, it was a Phase IIb open-label pharmacokinetic/pharmacodynamic (PK/PD) study with no comparator. It

included 25 subjects with Crohn’s treated with EPANOVA 4g/day. The primary objective of the study was to characterize the pharmacokinetic and pharmacodynamics of Epanova in subjects with Crohn’s disease. Laboratory safety evaluations included hematology, and serum chemistry and were performed at the following visits: Visit 1 (Screening, Week -1), Visit 4 (Week 30), and Visit 5 (Week 52).

EPIC-1E (TP0307) was the long-term open-label extension study for EPIC-1, EPIC-2, and EPIC-3, it involved 81 subjects with Crohn’s disease who received EPANOVA 4g/day for up to 3 years. Laboratory safety tests included hematology, and serum chemistry and were performed at the following visits: Visit 1, Visit 3 (Month 12), and Visit 5 (Month 24).

In summary, in the Crohn’s dataset there were 432 subjects with Crohn’s disease who received EPANOVA 4g/day and 372 subjects with Crohn’s disease who received placebo.

Safety parameters assessed in the therapeutic confirmatory trials are addressed in Section 7 of this review.

Table 3 below categorizes the clinical trials conducted based on clinical phase.

Table 3: Listing of Clinical Trials by Clinical Phase

	N	Population	Duration
Phase I studies			
SPC 275-4	73	Healthy subjects	6 weeks
OM-EPA-006	52	Healthy subjects	2-3 weeks based on cohort
OM-EPA-007	52	Healthy subjects	28 days
Phase II and IIb studies			
OM-EPA-001	54	Healthy subjects	23 days
TP0309 (EPIC-3)	25	Patients in remission from Crohn’s	52 weeks
Phase III studies			
OM-EPA-003 (EVOLVE)	399	Patients with Severe hypertriglyceridemia	12 weeks
OM-EPA-004 (ESPRIT)	646	Patients with Persistent Hypertriglyceridemia and High-Risk for Cardiovascular Disease	6 weeks
TP0307 (EPIC-1)	374	Patients with Crohn’s disease	52 weeks
TP0308 (EPIC-2)	379	Patients with Crohn’s disease	58 weeks
TP0307 Extension	82	Patients with Crohn’s	36 months

(EPIC-1E)		disease	
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Source: created by reviewer.

Reviewer’s note: No formal dose-response studies were conducted in Phase II; however in pool A multiple doses were tested. Only one Phase III pivotal study for severe hypertriglyceridemia, EVOLVE, was conducted, and the two studies in subjects with hypertriglyceridemia were of short duration. Longer studies were performed in subjects with Crohn’s disease but these studies are of limited relevance to this application given the different patient population.

6 Review of Efficacy

The efficacy and purported benefits of Epanova are addressed in Dr. Iffat Chowdury’s clinical efficacy review.

7 Review of Safety

Safety Summary

At Randomization, the control (olive oil) group and the Epanova treatment groups had similar demographic characteristics. Exposure to the investigational product in terms of both the number and type of subjects exposed was reasonably adequate. The overall safety assessment plan used in this development program was also adequate in terms of nature and frequency of assessments, as well as the range of doses, three doses, tested.

The duration of the Phase III trials conducted in subjects with hypertriglyceridemia, 12 weeks in study 003, the pivotal trial, and 6 weeks in study 004 was however relatively limited. This limitation of the Epanova drug development program was in part mitigated by the fact that additional controlled studies had been conducted in subjects with Crohn’s disease and these studies had a longer duration, one year. It should nevertheless be noted that the Crohn’s trials, albeit longer in duration than the studies conducted in subjects with hypertriglyceridemia, were conducted in a population of subjects with a high background prevalence of gastrointestinal and other symptoms, often of severe intensity. This important factor somewhat limits the quality and amount of safety information that may be extrapolated from the Crohn’s trials and applied to subjects with hypertriglyceridemia taking Epanova.

Treatment-emergent adverse events (TEAEs) were generally comparable between the olive oil group and the Epanova groups, and most adverse events (AE) in all treatment groups were generally tolerable, reversible, and self-limiting. The most frequently reported AEs for both the olive oil group and the Epanova groups included diarrhea,

nausea, abdominal pain, nasopharyngitis, and headache. Other common AEs included abdominal pain, dyspepsia, eructation, regurgitation, vomiting, fatigue, influenza, weight increased, arthralgia, and hypertension. The most frequently reported severe adverse events were due to cardiovascular reasons.

Serious adverse events (SAEs) were few and generally balanced among the study treatment groups, and the adverse events experienced by subjects in the trial were generally consistent with the established safety profile of Epanova. SAEs reported (one or more subjects) included cardiovascular and gastrointestinal events, hyperglycemia, bronchitis and osteoarthritis.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Refer to Section 5.1 of this review for a summary of the clinical trials pertinent to clinical safety. More detailed information about the individual studies can be found in Dr. Iffat Chowdhury's clinical review of efficacy.

7.1.2 Categorization of Adverse Events

All serious and non-serious AEs reported were recorded on a standardized AE-collection form that was included as part of the case report forms. If more than one sign or symptom was reported, a separate AE form was to be used for each. AE records included a description of the event, level of seriousness, onset and resolution date, severity, relationship to trial medication as judged by the investigator, any action taken, and outcome. For SAEs, a separate form was used in addition to the standard AE form.

AEs were defined as any undesirable medical event occurring in a subject in the clinical trial, whether or not related to the study drug. AEs were assessed at every study visit and were categorized by the investigator as mild, moderate, or severe; causality was assessed as probable, possible, or unlikely, according to commonly accepted criteria. SAEs were in accordance with FDA's definition, and included hospitalization, life threatening illness, and death. TEAEs were defined as an event that has onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment.

Based on the known safety and tolerability profile of this class of drugs, the applicant identified *a priori* certain medical events to be of special interest and developed specific reporting procedures for these events. These events included bleeding and hemorrhagic adverse events, gastrointestinal adverse events and hyperglycemia adverse events. This reviewer agrees with the applicant's rationale.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 14.1 for classification of adverse event data.

This reviewer compared a subset of the reported AE terms (verbatim terms) with the preferred terms used in the categorization of adverse events and found that in this subset the verbatim terms were appropriately mapped to the correct preferred terms.

7.1.3 Safety Endpoints

The safety endpoints routinely collected were as follows:

- Extent of Exposure to Investigational Product
- Adverse Events
 - Treatment-Emergent Adverse Events
 - Deaths and Other Serious Adverse Events
 - Other Severe or Significant AEs
- Withdrawals due to AEs
- Bleeding and Hemorrhagic Adverse Events,
- Gastrointestinal Adverse Events
- Physical Examination
- Vital Signs
- Electrocardiography (ECG)
- Pregnancy
- Clinical Laboratory Parameters
 - Hematology Parameters
 - Biochemistry Parameters
 - Lipid Parameters
 - Urinalysis.

7.2 Adequacy of Safety Assessments

This reviewer focused on the Hypertriglyceridemia, Placebo-Controlled dataset to derive an estimate the incidence of AEs. This dataset includes OM-EPA-003 (EVOLVE) and OM-EPA-004 (ESPRIT), of 12 weeks and 6 weeks duration, respectively (Pool A).

In addition, the Crohn's disease dataset was reviewed as well, because it contained useful supportive evidence on the safety of Epanova. The Crohn's dataset included two controlled studies, TP0307 (EPIC-1) and TP0308 (EPIC-2) of 52 and 58 weeks duration, and two uncontrolled studies, TP0309 (EPIC-3) and TP0307 (EPIC-1E) of 52 and up to 3 years duration, respectively.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall, 1343 subjects were exposed to Epanova and 844 subjects were exposed to control substances for a total of 2187 subjects in ten clinical studies. Table 4 below reports the extent of exposure as duration and dosage.

Table 4: Overall Extent of Exposure to Study Drug

Clinical Review – Safety
 Giovanni Cizza, MD, PhD, MHSc
 NDA 205060
 EPANOVA (omega-3-carboxylic acids)

Study Type Study No.	EPANOVA Dosage	EPANOVA Duration	Number of Subjects	
			EPANOVA	Control ^a
Clinical pharmacology/pharmacokinetics				
SPC 275-4	2 to 8 g/day	43 days	2 × 1 g/day SGC (n = 12) 2 × 2 g/day SGC (n = 12) 2 × 4 g/day SGC (n = 12) 4.5 g/day ^{(b) (4)} (n = 12)	MaxEPA 9 g/day capsules (n = 13) Placebo capsules (n = 12)
OM-EPA-001 (ECLIPSE) ^b	4 g/day	Single dose x 4	54	54
OM-EPA-006 ^c	4 g/day	3 weeks	26	26
OM-EPA-007 ^d	4 g/day	2 weeks	52	52
Total			180	157
Hypertriglyceridemia				
OM-EPA-003 (EVOLVE)	2, 3, or 4 g/day	12 weeks	100 (2 g) 101 (3 g) 99 (4 g)	99
OM-EPA-004 (ESPRIT)	2 or 4 g/day	6 weeks	215 (2 g) 216 (4 g)	215
Total			731	314
Crohn's disease				
Controlled				
TP0307 (EPIC-1)	4 g/day	52 weeks	187	184
TP0308 (EPIC-2)	4 g/day	58 weeks	189	188
Uncontrolled				
TP0309 (EPIC-3)	4 g/day	52 weeks	25	0
TP0307 (EPIC-1E)	4 g/day	Up to 3 years	81 ^e	
Total			432 ^f	372
Total in all studies			1343 ^f	844
^a = Control = MaxEPA caps (n = 13) and placebo (n = 12) in SPC 275-4, Lovaza in ECLIPSE and OM-EPA-006, simvastatin and acetylsalicylic acid in OM-EPA-007, placebo (olive oil) in EVOLVE, and ESPRIT, saturated fatty acids as triglycerides (Miglyol 812) in EPIC-1 and EPIC-2. ^b = Subjects were exposed twice to EPANOVA (once under fasting conditions and once under high-fat conditions) and twice to Lovaza (once under fasting conditions and once under high-fat conditions). ^c = Subjects received EPANOVA (days 8 to 28) and Warfarin (days 1 and 22) or Lovaza (days 1 to 14). ^d = Two-way crossover study of simvastatin + acetylsalicylic acid (ASA) with and without EPANOVA. ^e = EPIC-1E was the open-label extension for EPIC-1, EPIC-2, and EPIC-3; the subjects are therefore only counted once in the overall total. One additional subject in the EPIC-1E CSR (Subject 3211001901 [also referred to as Subject 001-01 in the ISS]) was summarized with the Safety Population in the CSR; however, this subject did not receive at least 1 dose of EPANOVA and is, therefore, not included in the ISS. ^f = A total of 31 subjects received placebo during EPIC-1, EPIC-2, or EPIC-3 and received EPANOVA during EPIC-1E. These 31 subjects are counted in both the EPANOVA total and the placebo total. CSR = clinical study report; ^{(b) (4)} ; ISS = Integrated Safety Summary; SGC = soft gelatin capsule Source: SPC 275-4, Table 1.1.2; OM-EPA-001, Section 12.1; OM-EPA-006, Section 12.1; OM-EPA-007, Section 12.1; OM-EPA-003, Table 11.1.1; OM-EPA-004, Table 11.1.1; EPIC-1, Section 7; EPIC-2, Section 7; EPIC-3, Section 8; EPIC-1E, Section 7.				

Source: from Sponsor, Table 2.7.4-1, Summary of Clinical Safety, pag. 14.

Table 5: Exposure by Treatment in Pool A (Studies OM-EPA 003 and OM-EPA-004)

Overall Exposure (days)	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99)	EPANOVA (N = 300)	Olive Oil (N = 215)	EPANOVA (N = 431)	Olive Oil (N = 314)	EPANOVA (N = 731)
Mean (SD)	81.5 (12.31)	78.1 (19.47)	41.7 (4.15)	41.3 (5.73)	54.2 (20.04)	56.4 (22.43)
Median	84.0	84.0	42.0	42.0	42.0	43.0
Min, Max	25.0, 114.0	1.0, 115.0	1.0, 50.0	1.0, 54.0	1.0, 114.0	1.0, 115.0
Max = maximum; Min = minimum; SD = standard deviation						
Source: Table 2.1.1.1						

Source: from Sponsor, Table 2.7.4-2, Summary of Clinical Safety.

In study 003, the mean duration of exposure was 81 days for Olive Oil and 78 days for EPANOVA.

Table 6 summarizes the compliance with the study drug for Study 003.

Table 6: Compliance with Investigational Product, Study 003, Safety Population

	Olive Oil N=98	Epanova 2g N=98	Epanova 3g N=97	Epanova 4g N=99	Total N=392
Overall Compliance (%)					
Mean (SD)	98.4 (4.12)	96.9 (9.20)	97.0 (10.95)	96.9 (10.07)	97.3 (8.97)
Median	100.0	100.0	100.0	100.0	100.0
Min, Max	67.1, 104.9	25.0, 109.0	0.0, 110.3	19.0, 115.4	0.0, 115.4
At Least 80% Compliant					
	97 (98.0%)	95 (95.0%)	95 (94.1%)	94 (94.9%)	381 (95.5%)

Source: created by reviewer based on Table 14.1.3.1, Clinical Study Report.

Across the different study groups, the mean percent of compliant subjects ranged between 97% and 98% and the percent of subjects at least 80% compliant ranged from 94% to 98%.

Table 7 summarizes the compliance with the study drug for Study 004

Table 7 Compliance with Investigational Product, Study 004, Safety Population

	Olive Oil N=213	Epanova 2g N=214	Epanova 4g N=215	Total N=642
Overall Compliance (%)				
Mean (SD)	97.5 (8.21)	96.8 (11.55)	96.2 (11.32)	96.8 (10.47)
Median	100.0	100.0	100.0	100.0
Min, Max	18, 114	8, 110	19, 103	8, 144
At Least 80% Compliant				
Mean (SD)	208 (97.7)	208 (97.2)	206 (95.8)	622 (96.9)

Source: created by reviewer based on Table 14.1.5, Clinical Study Report.

Across the different study groups, the mean percent of compliant subjects ranged between 96% and 97% and the percent of subjects at least 80% compliant ranged from 96% to 98%.

Reviewer’s note: Both in Study 003 and in Study 004 the compliance with study drug was satisfactory.

Table 8: Exposure by Dose Level in Pool A (Studies OM-EPA 003 and OM-EPA 004)

Overall Exposure (days)	Olive Oil (N = 314)	EPANOVA 2 g (N = 315)	EPANOVA 3 g (N = 101)	EPANOVA 4 g (N = 315)
Mean (SD)	54.2 (20.04)	53.4 (20.98)	75.8 (22.60)	53.2 (20.66)
Median	42.0	42.0	84.0	42.0
Min, Max	1.0, 114.0	1.0, 100.0	1.0, 115.0	1.0, 97.0
Max = maximum; Min = minimum; SD = standard deviation Source: Table 2.1.2.1				

Source: from Sponsor, Table 2.7.4-3, Summary of Clinical Safety.

In Pool A, the mean duration of exposure was 42 days for Olive Oil and 42 days for Epanova 2g and Epanova 4g. In both studies, the duration of exposure was comparable for Olive Oil and for Epanova.

Table 9 summarizes the demographic characteristics of the patients in the Hypertriglyceridemia, Placebo-Controlled Dataset

Table 9: Demographic Characteristics in Pool A (Studies OM-EPA 003 and OM-EPA 004)

Demographic Characteristics	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99)	EPANOVA (N = 300)	Olive Oil (N = 215)	EPANOVA (N = 431)	Olive Oil (N = 314)	EPANOVA (N = 731)
Age (years)						
Mean (SD)	50.8 (10.59)	51.7 (9.85)	61.5 (9.64)	60.5 (9.59)	58.1 (11.13)	56.9 (10.61)
Median	49.0	52.0	62.0	60.0	59.0	57.0
Min, Max	31, 80	24, 75	40, 89	35, 85	31, 89	24, 85
Age, n (%)						
< 65 years	88 (88.9)	272 (90.7)	124 (57.7)	279 (64.7)	212 (67.5)	551 (75.4)
≥ 65 years	11 (11.1)	28 (9.3)	91 (42.3)	152 (35.3)	102 (32.5)	180 (24.6)
Race, n (%)						
American Indian	0	1 (0.3)	1 (0.5)	1 (0.2)	1 (0.3)	2 (0.3)
Asian	4 (4.0)	19 (6.3)	3 (1.4)	4 (0.9)	7 (2.2)	23 (3.1)
Black or African American	0	3 (1.0)	10 (4.7)	12 (2.8)	10 (3.2)	15 (2.1)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.5)	0	1 (0.3)	0
White	95 (96.0)	276 (92.0)	197 (91.6)	411 (95.4)	292 (93.0)	687 (94.0)
Multiple	0	0	2 (0.9)	1 (0.2)	2 (0.6)	1 (0.1)
Other	0	1 (0.3)	1 (0.5)	2 (0.5)	1 (0.3)	3 (0.4)
Sex, n (%)						
Male	77 (77.8)	230 (76.7)	122 (56.7)	260 (60.3)	199 (63.4)	490 (67.0)
Female	22 (22.2)	70 (23.3)	93 (43.3)	171 (39.7)	115 (36.6)	241 (33.0)
Statin or CAI use, n (%)						
User	34 (34.3)	104 (34.7)	214 (99.5)	431 (100.0)	248 (79.0)	535 (73.2)
Non-user	65 (65.7)	196 (65.3)	1 (0.5)	0	66 (21.0)	196 (26.8)
Diabetes, n (%)						
Yes	31 (31.3)	120 (40.0)	156 (72.6)	306 (71.0)	187 (59.6)	426 (58.3)
No	68 (68.7)	180 (60.0)	59 (27.4)	125 (29.0)	127 (40.4)	305 (41.7)

CAI = cholesterol absorption inhibitor; Max = maximum; Min = minimum; SD = standard deviation
Source: [Table 1.2.1.1](#)

Source: from Sponsor, Table 2.7.4-5, Summary of Clinical Safety.

In study 003 mean age overall was 51, and subjects in the Olive Oil group were on average one year younger than subjects in the Epanova group. Overall, approximately

10% of subjects were older than 65 years with a slight difference between groups: the proportion of subjects older than 65 was slightly larger, 11% in the Olive Oil group than in the Epanova group 9%.

In study 004 mean age overall was 61 and subjects in the Olive Oil group were on average one year older than subjects in the Epanova group. Overall, approximately 40% of subjects were older than 65 years with a slight difference between groups: the proportion of subjects older than 65 was slightly larger in the Olive Oil group than in the Epanova group.

Table 10: Age and Sex Sub-Groups in Study 003

Age Group	Placebo	Epanova 2g	Epanova 3g	Epanova 4g
<65	88 (88.89%)	92 (92.00%)	97 (96.04%)	83 (83.84%)
>=65	11 (11.11%)	8 (8.00%)	4 (3.96%)	16 (16.16%)
Subjects	99 (100.00%)	100 (100.00%)	101 (100.00%)	99 (100.00%)
Sex				
F	22 (22.22%)	20 (20.00%)	22 (21.78%)	28 (28.28%)
M	77 (77.78%)	80 (80.00%)	79 (78.22%)	71 (71.72%)
Subjects	99 (100.00%)	100 (100.00%)	101 (100.00%)	99 (100.00%)

Source: created by reviewer.

In study 003 the lowest proportion of subjects older than 65 was reported in the Epanova 3g group, followed by the Epanova 2g group, the Olive Oil group, and the Epanova 4g group. The male/female proportion was approximately 4:1. Within sexes, there was a reasonably equal distribution of subjects in each group, when considering the relatively small sample of Study 003.

Table 11: Age and Sex Sub-Groups in Study 004

Age Group	Olive oil	Epanova 2 g	Epanova 4 g
<65 years	124 (57.67%)	138 (64.19%)	141 (65.28%)
>=65 years	91 (42.33%)	77 (35.81%)	75 (34.72%)
Subjects	215 (100.00%)	215 (100.00%)	216 (100.00%)
Sex			
F	93 (43.26%)	92 (42.79%)	79 (36.57%)
M	122 (56.74%)	123 (57.21%)	137 (63.43%)
Subjects	215 (100.00%)	215 (100.00%)	216 (100.00%)

Source: created by reviewer.

In study 004 the lowest proportion of subjects older than 65 was reported in the Epanova 4g group, followed by the Epanova 2g group, and the Olive Oil group.

The male/female proportion was approximately 60/40. Similarly to study 003, in Study 004 within sexes, there was a reasonably equal distribution of subjects in each group, when considering the relatively small sample of Study 004.

In study 003 approximately 35% (138/399) of subjects were statin users and 38% (151/399) had diabetes. There were fewer subjects with diabetes in the olive oil group than in the Epanova group (31% vs. 40%).

In study 004, as per inclusion criteria, subjects were users of statins or cholesterol absorption inhibitor (CAI) and 2/3 of subjects had diabetes, with a similar distribution in the olive oil group and in the Epanova group (73% vs. 71%).

Reviewer’s note: According to the 2001-2006 NHANES survey [Am J Cardiol 2011; 107:891-897] approximately 10% of subjects ≥ 60 (no data were published using 65 year old as a cut-off but the prevalence in this age group is likely to be similar if not greater) have TG levels between 500-2000 mg/dL. Older subjects are more likely to have more comorbidities and concomitant medications. Therefore, In the opinion of this reviewer, the absolute number (28) of subjects older than 65 with severe hypertriglyceridemia that have been exposed to the study drug and the amount of information gathered on this age groups is relatively limited in light of the prevalence of this condition in this age group. In addition, the preponderance of white subjects in both studies and of white subjects and male subjects in study 003 may raise the issue of generalizability of these findings to female subjects and subjects of non-White ethnicity.

Subjects with Crohn’s disease

Table 12: Demographic characteristics in Pool B (Studies EPIC-1, EPIC-2, and EPIC 1E)

		Placebo (N=372)	Epanova 4g (N=432)
Age (years)	n	372	432
	Mean (SD)	38.5 (13.30)	38.8 (14.57)
	Median	37.0	36.0
	Min, Max	18, 76	18, 82
Age, n (%)	< 65 years	357 (96.0)	403 (93.3)
	\geq 65 years	15 (4.0)	29 (6.7)
Race, n (%)	Asian	0	1 (0.2)
	Black	1 (0.3)	1 (0.2)
	Caucasian	365 (98.1)	425 (98.4)
	Hispanic	1 (0.3)	0
	Other	5 (1.3)	5 (1.2)
Sex, n (%)	Male	154 (41.4)	194 (44.9)
	Female	218 (58.6)	238 (55.1)

Source: Integrated Summary of Safety, Table 1.2.3.1

Average age was 38 year old, there were very few subjects, approximately 5% older than 65, most subjects were Caucasian and there was a small preponderance of female vs. male subjects.

7.2.2 Concomitant Diseases in Exposed Subjects

Concomitant illnesses were recorded for all study subjects as part of the medical history. In study 003 approximately 38% of subjects had a diagnosis of type 2 diabetes whereas in study 004 approximately 71% of subjects had a diagnosis of type 2 diabetes.

7.2.3 Concomitant Medications in Exposed Subjects

Prior medications were defined as those used prior to and stopped before the first dose of investigational product. Concomitant medications were defined as those used during the double-blind treatment period. In study 003, approximately 1/3 of subjects were on statins or CAI.

In study 003:

Permitted medications included:

- Statins, cholesterol absorption inhibitors (CAI) or statin-CAI combinations (cannot be started at any time after Visit 1).
- Estrogens (other than topical estrogens for local vaginal symptoms), progestins and androgens (cannot be started at any time after Visit 1).
- Tamoxifen (cannot be started at any time after Visit 1).

Prohibited medications included:

- Bile acid sequestrants, fibrates, niacin (other than niacin-containing multiple vitamins <200 mg), omega-3 drugs or supplements.
- Dietary fiber supplements, red rice yeast supplements, garlic supplements, soy isoflavone supplements, sterol/stanol products, or policosanols.
- Oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/asthma) or anabolic steroids.
- Anticoagulants (e.g. warfarin [Coumadin®], coumarin, heparin, enoxaparin, clopidogrel).

Subjects could continue use of statins or CAIs or their combination during the study provided they were on a stable dose for a sufficient period of time.

In study 004

Permitted medications included:

- Stable use (defined as no change in treatment or dosage during the 4 weeks prior to Visit 1) of medications for hypertension, Type 2 diabetes mellitus (HbA1c or thyroid disease (TSH $\leq 1.5 \times \text{ULN}$). Changes to the medication regimens to treat these conditions permitted after Visit 1 as clinically indicated based on investigator discretion.
- Lipid altering drug regimens if stable for at least 4 weeks prior to Visit 1.
- Medications for hypertension, type 2 diabetes mellitus (HbA_{1c} $\leq 10\%$), thyroid disease; all oral, patch, etc. hormonal or selective estrogen receptor modulator contraceptives.
- Inhaled or intranasal corticosteroids, estrogens, tamoxifen, or progestins, topical estrogens for local vaginal symptoms and daily use of testosterone.

Prohibited medications included:

- Bile acid sequestrants, fibrates, or niacin or its analogues (greater than 200 mg/d)
- Simvastatin 80 mg or Vytorin 10/80 mg
- EPA or DHA products, fish oil, or medications (e.g., Lovaza) or investigational drugs (e.g., AMR101) containing EPA or DHA
- Any supplement for the purpose of lowering plasma cholesterol (e.g., red rice yeast supplements)
- Weight loss drugs (including over-the-counter)
- Erythromycin, telithromycin, clarithromycin, cyclosporine, itraconazole, ketoconazole, protease inhibitors, or nefazodone
- Anticoagulants (e.g. warfarin, coumarin, heparin, Pradaxa® or enoxaparin)

- Oral or injected corticosteroids (other than intranasal or inhaled steroids used for allergies/asthma)
- Grapefruit juice > 750 mL/day
- Insulin.

Reviewer’s note: The Sponsor provided the information on medications in appendices listed by individual subject. This reviewer performed a qualitative analysis of the concomitant medications by examining the medications that each individual subject took: the medications listed appeared consistent with the patient population.

7.3 Major Safety Results

7.3.1 Deaths

A total of three deaths were reported in the studies submitted with this NDA. One death occurred in the EVOLVE study in a 60 year old male subject treated with EPANOVA 3g who develop pulmonary embolism, and two deaths were reported in the Crohn’s disease dataset, one in a 56 year old female subject treated with placebo who develop metastatic adenocarcinoma and another in a 68 year old female subject treated with Epanova 4g who develop liver metastases (see Table 13).

Table 13: Listing of Deaths in Overall Integrated Dataset

System Organ Class/ Preferred Term	Subject ID#/Study	Age/Gender	Treatment Group	Time since Start of Study
Pulmonary embolism	104-050/OM-EPA-003 (EVOLVE Study)	60 yo male	Epanova 3 g	11 days
Metastatic adenocarcinoma	211-17 EPIC-2	56 yo female	Placebo	125 days
Liver metastasis of malignant melanoma	11 01 001 104 EPIC-1	68 yo female	Epanova 4g	505 days

Source: created by reviewer.

Subject: 104-050
Study: EVOLVE (Hyperlipidemia Study)
Treatment: EPANOVA 3g

“**Subject 104-050** was a 60 year old male with a history of hypertriglyceridemia, hypertension, and diabetes mellitus who died of a pulmonary embolus. Medical history also included chronic prostatitis,

depression, and adrenal adenoma. The subject was screened on (b) (6). On (b) (6) he was randomized to receive oral Epanova 3 grams daily. Concomitant medications included Cardura (doxazosin mesylate), Glucobay (acarbose), Lescol (fluvastatin sodium) XL, Rivotril (clonazepam), Tallitron, and Zyprexa (olanzapine). He discontinued Lipidil Supra (fenofibrate), which he had been taking for 10 years. On (b) (6), the subject suffered sudden death. The physician on duty considered the cause of death pulmonary embolism. No autopsy was performed, and additional medical information was not available. The investigator considered the death not related to Epanova. The Sponsor considered the death unrelated to Epanova and possibly related to his underlying hypertriglyceridemia or possibly to long term use of fenofibrate”

Reviewer’s note: This Reviewer believes that the death was likely caused by underlying cardiovascular pathology, hypertriglyceridemia, and hypertension suffered by the patient, rather than possibly being related to treatment with Epanova 3g.

Subject: 211-17
Study: EPIC-2
Treatment: Placebo

“Subject 211-17, who received placebo from (b) (6) to (b) (6), was a 56-year-old Caucasian female who experienced a fatal malignancy (metastatic adenocarcinoma) that started on the last day of study drug (b) (6). The investigator assessed the fatal TEAE as unlikely related to study drug. The subject (metastatic adenocarcinoma) that started after her last day of study drug (b) (6) and liver biopsy revealed metastatic adenocarcinoma”.

Source: from Sponsor, Summary of Clinical Safety, pag.36

Reviewer’s note: This Reviewer concluded that the death was most likely due to the metastatic adenocarcinoma and the related pathology.

In addition, a death took place in a subject 7 months after completion of study drug. For this reason, the Sponsor did not list this event in the safety database. This Reviewer agrees with the Sponsor’s rationale. The narrative from the Sponsor is provided below:

Subject 11 01 001 104 (Malignant melanoma; Day of death: Day 633) This 68-year old female patient was enrolled in the EPIC-1 TP0307 study and received her first dose of study medication on (b) (6). The first CD symptoms occurred in 1974. CD was diagnosed by a physician in Jul-1990 and confirmed on 29-Jun-2000. The patient's medical history included intestinal tuberculosis, gastric ulcer, reflux oesophagitis, appendectomy, sterilization and laparotomy. On 12-Sep-2003 the patient was diagnosed with a malignant melanoma by an external dermatologist. The melanoma was on the back, right side. A resection of the tumor was carried out on (b) (6). Sentinel lymph node was also resected, but showed no malignant components. The patient recovered without sequelae on (b) (6) and was discharged from hospital on (b) (6). In the opinion of the investigator, the causal relationship of the event to the study medication was considered to be unrelated. Study drug was resumed and continued following the diagnosis of malignant melanoma until (b) (6), when the subject completed post-treatment telephone visit 16 (final study visit). No recurrence of melanoma was reported at the final study visit. The investigator learned of this subject's death due to liver metastases from the malignant melanoma. The metastases were discovered at the beginning of Dec-2004 and the subject died (b) (6).

Source: from Sponsor, page 73, Clinical Study Report, EPIC-1

Reviewer's note: It is the opinion of this reviewer that the death was likely due to liver metastasis secondary to malignant melanoma. Nevertheless this subject had been randomized to the Epanova 4g group; because this subject had been exposed to the study drug, the remote and biologically not plausible possibility that the death was related to the study drug cannot be formally excluded.

7.3.2 Nonfatal Serious Adverse Events

A serious adverse event (SAE) was defined any adverse experience that resulted in any of the following: death, life-threatening adverse event, persistent or significant disability, in-patient hospitalization, or congenital anomaly or birth defect.

Serious adverse events were also reported by the Sponsor by System Organ Class and preferred terms, as indicated below:

Pool A: Subjects with Hypertriglyceridemia

Table 14: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term in Pool A (Studies OM-EPA 003 and OM-EPA 004)

Clinical Review – Safety
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 NDA 205060
 EPANOVA (omega-3-carboxylic acids)

System Organ Class Preferred Term	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n (%)	EPANOVA (N = 300) n (%)	Olive Oil (N = 215) n (%)	EPANOVA (N = 431) n (%)	Olive Oil (N = 314) n (%)	EPANOVA (N = 731) n (%)
Any treatment-emergent SAE	2 (2.0)	5 (1.7)	3 (1.4)	4 (0.9)	5 (1.6)	9 (1.2)
Cardiac disorders	1 (1.0)	3 (1.0)	0	1 (0.2)	1 (0.3)	4 (0.5)
Angina pectoris	0	2 (0.7)	0	0	0	2 (0.3)
Coronary artery disease	0	1 (0.3)	0	1 (0.2)	0	2 (0.3)
Myocarditis	1 (1.0)	0	0	0	1 (0.3)	0
Musculoskeletal and connective tissue disorders	0	0	0	2 (0.5)	0	2 (0.3)
Musculoskeletal chest pain	0	0	0	1 (0.2)	0	1 (0.1)
Osteoarthritis	0	0	0	1 (0.2)	0	1 (0.1)
Gastrointestinal disorders	1 (1.0)	0	1 (0.5)	1 (0.2)	2 (0.6)	1 (0.1)
Diverticular perforation	0	0	0	1 (0.2)	0	1 (0.1)
Abdominal pain	1 (1.0)	0	0	0	1 (0.3)	0
Intestinal obstruction	0	0	1 (0.5)	0	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	0	0	0	1 (0.1)
Pulmonary embolism	0	1 (0.3)	0	0	0	1 (0.1)
Surgical and medical procedures	0	1 (0.3)	0	0	0	1 (0.1)
Implantable defibrillator insertion	0	1 (0.3)	0	0	0	1 (0.1)
Infections and infestations	0	0	1 (0.5)	0	1 (0.3)	0
Bronchitis	0	0	1 (0.5)	0	1 (0.3)	0
Metabolism and nutrition disorders	0	0	1 (0.5)	0	1 (0.3)	0
Hyperglycaemia	0	0	1 (0.5)	0	1 (0.3)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event
 Note: AEs were classified according to System Organ Class and Preferred Term using MedDRA version 14.1.
 Source: [Table 3.7.1.1](#)

Source: from Sponsor, Table 2.7.4-17, Summary of Clinical Safety.

As noted in Table 14, the incidence of TE SAEs was 1.2% in the Epanova group and 1.6% in the Olive Oil group. Overall, there were 14 SAEs reported out of a total of 1045 subjects in pool A. This number appears quite limited in this specific patient population, even when taking into account the relatively short duration of Study 003 and Study 004.

Table 15 further characterizes the serious AEs in Pool A by age, sex, treatment group, AE term, day onset, and discontinuation.

Table 15: Serious AEs in Study 003 and 004

Study	Subject #	Age/Sex	Treatment Group	AE term	Study day onset	Drug discontinuation Y/N
003	004-020	56/F	Epanova 3g	CORONARY ARTERY DISEASE WITH CHEST PAIN	Day 1	Y
003	104-050	60/M	Epanova 3g	PULMONARY EMBOLISM	Day 10	Sudden death
003	104-059	37/M	Olive Oil	MYOCARDITIS	Day 72	N
003	105-028	62/M	Epanova 3g	ANGINA PECTORIS	Day 74	Y
003	109-011	31/M	Olive Oil	WORSENING OF HYPERLIPIDEMIA	Day 73	N
003	109-039	46/M	Epanova 2g	ANGINA	Day 72	N
003	142-009	64/M	Epanova 3g	REPLACEMENT OF IMPLANTABLE CARDIOVERTER DEFIBRILLATOR	Day 14	N
004	043-005	48/M	Olive Oil	BRONCHITIS	Day 17	N
004	044-014	72/M	Olive Oil	INTESTINAL OBSTRUCTION	Day 27	N
004	058-003	63/M	Olive Oil	HYPERGLICEMIA		N
004	045-004	64/M	Epanova 2g	MUSCOLOSKELETAL CHEST PAIN	Day 16	N
004	045-011	71/M	Epanova 2g	DIVERTICULAR PERFORATION	Day 6	N
004	092-015	63/M	Epanova 2g	OSTEOARTHRITIS	Day 19	Y
004	031-007	56/M	Epanova 4g	CORONARY ARTERY DISEASE	Day 16	Y

Source: created by reviewer.

In Study 003 there were a total of seven SAEs. These SAEs were predominantly of cardiovascular nature which is consistent with the type of morbidities frequently reported in the population studied, subjects with hypertriglyceridemia. Most of the SAEs, six out of seven, were reported in male subjects, five of the seven SAEs were reported in subjects taking Epanova 2g or Epanova 3g, and the remaining two in subjects on olive oil. In Study 004 seven SAEs were reported. The nature of the SAEs in study 004 was more heterogeneous than in study 003, possibly because of the different nature of study population in study 004, and included cardiovascular events, as well as gastrointestinal

events and osteoarthritis. All the seven SAEs were reported in male subjects; three were reported in subjects taking olive oil and the rest in subjects taking Epanova.

Table 16 characterizes the SAEs in Pool A in terms of individual doses.

Table 16: Treatment Emergent Serious Adverse Events by Dose level, System Organ Class and Preferred Terms in Pool A (OM-EPA-003 and OM-EPA-004)

System Organ Class Preferred Term	Olive Oil (N=314) n (%)	Epanova 2g (N=315) n (%)	Epanova 3g (N=101) n (%)	Epanova 4g (N=315) n (%)
Any Treatment Emergent SAE	5 (1.6)	4 (1.3)	4 (4.0)	1 (0.3)
CARDIAC DISORDERS	1 (0.3)	1 (0.3)	2 (2.0)	1 (0.3)
CORONARY ARTERY DISEASE	0	0	1 (1.0)	1 (0.3)
ANGINA PECTORIS	0	1 (0.3)	1 (1.0)	0
MYOCARDITIS	1 (0.3)	0	0	0
GASTROINTESTINAL DISORDERS	2 (0.6)	1 (0.3)	0	0
ABDOMINAL PAIN	1 (0.3)	0	0	0
DIVERTICULAR PERFORATION	0	1 (0.3)	0	0
INTESTINAL OBSTRUCTION	1 (0.3)	0	0	0
INFECTIONS AND INFESTATIONS	1 (0.3)	0	0	0
BRONCHITIS	1 (0.3)	0	0	0
METABOLISM AND NUTRITION DISORDERS	1 (0.3)	0	0	0
HYPERGLYCAEMIA	1 (0.3)	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	2 (0.6)	0	0
MUSCULOSKELETAL CHEST PAIN	0	1 (0.3)	0	0
OSTEOARTHRITIS	0	1 (0.3)	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (1.0)	0
PULMONARY EMBOLISM	0	0	1 (1.0)	0
SURGICAL AND MEDICAL PROCEDURES	0	0	1 (1.0)	0
IMPLANTABLE DEFIBRILLATOR INSERTION	0	0	1 (1.0)	0

Source: from Sponsor, Table 3.7.2.1, Integrated Summary of Safety.

Reviewer’s note: The overall incidence of SAEs in subjects with hypertriglyceridemia was quite low, 1.3% and was similar between the olive oil group, 1.6% and the Epanova groups, 1.2%. Of note, the incidence of SAEs in the Epanova 3g group was four-fold higher, 4% than in any other group, including 4g. Since the absolute number of SAEs was small (n=4), it is hard to draw any firm conclusion from this observation.

Pool B Subjects with Crohn’s disease

Table 17: Treatment-Emergent Serious Adverse Events Occurring in >1 Subject by System Organ Class and Preferred Terms in Pool B (Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

System Organ Class Preferred Term	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any treatment-emergent SAE	33 (8.9)	51 (11.8)
Gastrointestinal disorders	21 (5.6)	29 (6.7)
Crohn's disease	7 (1.9)	16 (3.7)
Intestinal obstruction	4 (1.1)	4 (0.9)
Small intestinal obstruction	2 (0.5)	4 (0.9)
Abdominal pain	1 (0.3)	2 (0.5)
Subileus	2 (0.5)	1 (0.2)
Pancreatitis	2 (0.5)	0
Infections and infestations	2 (0.5)	17 (3.9)
Anal abscess	1 (0.3)	4 (0.9)
Appendicitis	0	2 (0.5)
Gastroenteritis	0	2 (0.5)
Pregnancy, puerperium and perinatal conditions	5 (1.3)	3 (0.7)
Pregnancy	5 (1.3)	3 (0.7)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event Note: AEs were coded using MedDRA version 14.1. Source: Table 3.7.3.1		

Source: from Sponsor, Table 2.7.4-18, Summary of Clinical Safety.

The incidence of treatment-emergent SAEs was not meaningfully different from a clinical point of view in the placebo group (9%; N=33) vs. the Epanova 4g group (12%; N=51). The SAEs reported were mostly of gastrointestinal nature and were typical of those observed in subjects with Crohn's disease. No differences in the incidence of SAEs were evident between subjects on placebo and subjects on Epanova 4g.

7.3.3 Dropouts and/or Discontinuations

Pool A: Subjects with Hypertriglyceridemia

Table 18 characterizes the number and percent of the subjects that completed the study, and of those who discontinued and the reasons for discontinuations.

Table 18: Subject Disposition in Pool A (Studies OM-EPA-003 and OM-EPA-004)

	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n(%)	EPANOVA (N = 300) n(%)	Olive Oil (N = 215) n(%)	EPANOVA (N = 431) n(%)	Olive Oil (N = 314) n(%)	EPANOVA (N = 731) n(%)
Completed study	94 (94.9)	270 (90.0)	210 (97.2)	413 (95.8)	304 (96.5)	683 (93.4)
Discontinued study	5 (5.1)	30 (10.0)	5 (2.3)	18 (4.2)	10 (3.2)	48 (6.6)
Adverse events	0	17 (5.7)	2 (0.9)	10 (2.3)	2 (0.6)	27 (3.7)
Non-compliance	0	0	1 (0.5)	1 (0.2)	1 (0.3)	1 (0.1)
Major protocol violation	0	3 (1.0)	0	1 (0.2)	0	4 (0.5)
Withdrawal by subject	1 (1.0)	4 (1.3)	0	5 (1.2)	1 (0.3)	9 (1.2)
Lost to follow-up	1 (1.0)	3 (1.0)	2 (0.9)	1 (0.2)	3 (1.0)	4 (0.5)
Other ^a	3 (3.0)	3 (1.0)	0	0	3 (1.0)	3 (0.4)

^a = Other reasons in the EPANOVA group included: triglyceride levels > 2000 mg/dL at 2 consecutive visits (2 subjects) and unable to remain in study because the subject was deported; other reasons in the placebo (olive oil) group (each in 1 subject) included, unable to remain in study due to taking a job abroad, elevated serum glucose, and triglyceride levels > 2000 mg/dL at 2 consecutive visits.
 Source: [Table 1.1.1.1](#) and [Table 1.3.1.1](#)

Source: from Sponsor Table 2.7.4-4 Integrated Summary of Safety.

Ninety-four percent (987/1045) of the subjects enrolled in Pool A completed the study: 91% (364/399) in study 003 and 96% (623/646) in study 004. In both studies, a slightly greater proportion of subjects completed study in the olive oil group vs. the Epanova group (003: 94.9% vs.90.0%; 004: 97.2% vs. 95.8%)

The proportion, five and half percent of subjects (58/1045, 5.5%) who did not complete study was quite limited. When comparing the Olive Oil and the Epanova groups, across studies a relatively smaller percentage of subjects discontinued study in the Olive Oil group vs. the Epanova group (003: 5% vs. 10%; 004: 2.3% vs. 4.2%) so that the combined discontinuation rate in the Olive Oil group (3.2%) was half that in the Epanova group (6.6%).

Reviewer’s note: In general, the proportion of subjects who did not complete the study, 5.5% was acceptable. The overall discontinuation rate was twice smaller in the olive oil group, 3.2% vs. the Epanova group, 6.4%, likely because Epanova was less well tolerated than olive oil.

The difference, 91% vs. 96%, observed in the completion rate between 003 and 004 was likely due to the difference in the duration of these two studies, as well as to the differences in the populations studied.

Subject 105-028 (Epanova 3g; SAE of “angina pectoris”) was not included in Table 16. This subject was listed as having completed the study on (b) (6), but this was study day 75, which was the date he was admitted to the hospital (and study drug discontinued) for angina pectoris.

Table 19 depicts the TEAEs leading to study drug discontinuation

Table 19: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation in > 1 Subject by System Organ Class and Preferred Term in Pool A (Studies OM-EPA-003 and OM-EPA-004)

System Organ Class Preferred Term	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n (%)	EPANOVA (N = 300) n (%)	Olive Oil (N = 215) n (%)	EPANOVA (N = 431) n (%)	Olive Oil (N = 314) n (%)	EPANOVA (N = 731) n (%)
Any TEAE ^a leading to study drug discontinuation	0	16 (5.3)	2 (0.9)	10 (2.3)	2 (0.6)	26 (3.6)
Gastrointestinal disorders	0	8 (2.7)	1 (0.5)	8 (1.9)	1 (0.3)	16 (2.2)
Diarrhoea	0	4 (1.3)	1 (0.5)	4 (0.9)	1 (0.3)	8 (1.1)
Nausea	0	2 (0.7)	0	3 (0.7)	0	5 (0.7)
Abdominal pain	0	2 (0.7)	0	2 (0.5)	0	4 (0.5)
Abdominal pain upper	0	3 (1.0)	0	1 (0.2)	0	4 (0.5)
Vomiting	0	1 (0.3)	0	3 (0.7)	0	4 (0.5)
Dyspepsia	0	0	0	3 (0.7)	0	3 (0.4)
Eructation	0	1 (0.3)	0	1 (0.2)	0	2 (0.3)
Cardiac disorders	0	2 (0.7)	0	1 (0.2)	0	3 (0.4)
Coronary artery disease	0	1 (0.3)	0	1 (0.2)	0	2 (0.3)
Metabolism and nutrition disorders	0	2 (0.7)	0	0	0	2 (0.3)
Diabetes mellitus	0	2 (0.7)	0	0	0	2 (0.3)

^a = Includes serious and nonserious TEAEs.
 AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
 Note: AEs were classified according to System Organ Class and Preferred Term using MedDRA version 14.1.
 Source: [Table 3.5.1.1](#)

Source: from Sponsor, Table 2.7.4-19, Summary of Clinical Safety.

The overall percent of TEAEs leading to study drug d/c was smaller in the olive oil group than in the Epanova group (0.6% vs. 3.6%), both in study 003 (0% vs. 5.3%) and in study 004 (0.9% vs. 2.3%). Approximately 2/3 (17/28) of the TEAEs leading to study drug d/c were reported for the gastrointestinal system, the remaining TEAEs were reported in the cardiac disorders and in the metabolism and nutrition disorders SOCs.

Reviewer's note: Overall, there was a preponderance of AEs leading to study drug discontinuation in the Epanova group compared to the Olive Oil group.

Table 20 reports the overall incidence of adverse events in study 003.

Table 20: Overall incidence of Adverse Event

Adverse Event [1]	Olive Oil N=99	Epanova 2 g N=100	Epanova 3 g N=101	Epanova 4 g N=99	p-value [2]
Subject With Any AE, n (%)	26 (26.3%)	40 (40.0%)	43 (42.6%)	44 (44.4%)	0.036
Serious, n (%)	2 (2.0%)	1 (1.0%)	4 (4.0%)	0 (0.0%)	
Severe, n (%)	5 (5.1%)	2 (2.0%)	3 (3.0%)	1 (1.0%)	
Related to IP, n (%) [3]	3 (3.0%)	18 (18.0%)	17 (16.8%)	25 (25.3%)	
Caused Discontinuation, n (%)	0 (0.0%)	5 (5.0%)	7 (6.9%)	5 (5.1%)	

Source: Table 14.3.1.1, Listing 16.2.7.1.

AE = adverse event; i.e. adverse events experienced after first dose of investigational product. IP = Investigational Product. Percentages (%) = 100 x n/total number of N.

[1] If a subject experiences the same event more than once, or more than one event, only the occurrence with the highest degree of categorical relevance is tabulated.

[2] P-value generated by a Chi-Square Test comparing across all treatments.

[3] Related means possibly, probably, or definitely related.

Source: from 003 Clinical Study Report

Table 21 reports the TEAEs leading to study drug discontinuation divided by dose.

Table 21: Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by Dose Level, System Organ Class and Preferred Terms

Pool A: OM-EPA-003 and OM-EPA-004

System Organ Class Preferred Term	Olive Oil (N=314) n (%)	Epanova 2g (N=315) n (%)	Epanova 3g (N=101) n (%)	Epanova 4g (N=315) n (%)
Any TEAE Leading to Study Drug Discontinuation	2 (0.6)	7 (2.2)	7 (6.9)	12 (3.8)
GASTROINTESTINAL DISORDERS	1 (0.3)	4 (1.3)	3 (3.0)	9 (2.9)
DIARRHOEA	1 (0.3)	3 (1.0)	0	5 (1.6)
DYSPEPSIA	0	0	0	3 (1.0)
ABDOMINAL PAIN UPPER	0	1 (0.3)	1 (1.0)	2 (0.6)
NAUSEA	0	3 (1.0)	0	2 (0.6)
VOMITING	0	1 (0.3)	1 (1.0)	2 (0.6)
ABDOMINAL DISTENSION	0	0	0	1 (0.3)
ABDOMINAL PAIN	0	2 (0.6)	1 (1.0)	1 (0.3)
ERUCTATION	0	1 (0.3)	0	1 (0.3)
FLATULENCE	0	0	0	1 (0.3)
ABDOMINAL DISCOMFORT	0	1 (0.3)	0	0
IRRITABLE BOWEL SYNDROME	0	0	1 (1.0)	0
METABOLISM AND NUTRITION DISORDERS	0	0	0	2 (0.6)

Adverse Event Coding Dictionary: MedDRA version 14.1

Percentages are based on the number of safety subjects in each integrated analysis set.

An adverse event is considered to be treatment emergent if the event started on or after the date of administration of the first dose of study drug.

A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

Source: Table 3.5.2.1, Integrated Summary of Safety.

The highest proportion of TEAEs leading to study drug d/c was observed in the Epanova 3g (6.9%) and the most common TEAEs leading to study drug d/c was diarrhea, observed in the Epanova 4g.

Reviewer's note: The highest incidence 6.9% of TEAEs leading to study d/c was reported at the 3g dose, rather than at the highest dose studied, 4g. Because of the relatively small size of each group and the smaller sample size of Epanova 3g, it is difficult to make any definitive conclusion from this observation which nevertheless appears counter-intuitive to this reviewer.

Table 22 lists the individual subjects who discontinued study drug due to TEAEs.

Table 22: Discontinuation of Study Drug Due to TEAEs

Study	Subject #	Age/Race/Sex	Treatment Group	Reason for d/c	Severity
003	004-020	56/white/female	Epanova 3g	Need for Plavix, prohibited medication	Severe (serious)
003	105-028	62/white/male	Epanova 3g	Angina pectoris	mild (serious)
003	001-002	68/black/male	Epanova 3g	Face edema	Moderate
003	003-002	63/white/male	Epanova 4g	Worsening of diabetes mellitus	Mild
003	003-004	40/white/female	Epanova 3g	Menorrhagia	Mild
003	004-034	48/white/male	Epanova 2g	Urticarial	Severe
003	008-008	49/white/female	Epanova 3g	Vomiting	Moderate
003	013-002	61/white/male	Epanova 4g	Diarrhea	Moderate
003	029-010	46/white/male	Epanova 4g	Upper abdominal pain	Moderate
003	099-003	60/white/male	Epanova 2g	Abdominal pain, nausea, headache, and diarrhea	Moderate
003	101-015	57/white/male	Epanova 3g	Dysgeusia and upper abdominal pain	Moderate
003	103-12	40/white/female	Epanova 4g	Diarrhea	Severe

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003	107-007	66/white/male	Epanova 2g	Upper abdominal pain	Mild
003	109-017	61/white/female	Epanova 2g	Weight pain	Mild
003	109-022	57/white/male	Epanova 4g	diabetes mellitus	Moderate
003	142-003	42/white/male	Epanova 3g	Exacerbation of irritable bowel syndrome	Moderate
003	143-005	47/white/male	Epanova 2g	Abdominal pain, nausea, and diarrhea	Moderate
004	008-015	59/white/male	Epanova 4g	Vomiting, diarrhea, and stomach pain	Moderate
004	010-038	52/white/female	Placebo (olive oil)	Diarrhea	Severe
004	014-003	54/white/female	Epanova 4g	Diarrhea, nausea and vomiting	Severe (diarrhea) Moderate (nausea and vomiting)
004	016-004	58/white/female	Epanova 4g	Abdominal cramping, abdominal bloating, and indigestion	Moderate
004	024-009	67/white/male	Epanova 4g	Belching, flatulence, dyspepsia	Mild (Belching, flatulence) Moderate (dyspepsi a)
004	031-007	56/white/male	Epanova 4g	Coronary artery disease	Severe (serious)
004	031-010	79/white/female	Placebo (olive oil)	Diffuse myalgia	Mild
004	032-028	64/white/male	Epanova 2g	Gastrointestinal distress	Moderate
004	056-002	61/white/female	Epanova 4g	Nausea	Moderate
004	072-026	63/white/female	Epanova 2g	Abdominal pain, diarrhea, nausea, and vomiting	Moderate
004	080-007	65/white/male	Epanova 4g	Diarrhea Dyspepsia	Moderate (diarrhea) Mild (dyspepsi

					a)
004	092-015	63/white/male	Epanova 2g	Worsening of osteoarthritis	Severe (serious)

Source: created by reviewer based on CSR 003 and CSR 004.

A total of 29 subjects (18 males; 11 females) experienced a TEAEs leading to discontinuation from study, most of these TEAEs took place in subjects taking Epanova, approximately 60% were of gastrointestinal nature, approximately 60% took place in male subjects, and 1/4 were severe in nature. In terms of severity, approximately 55% were of moderate intensity and the rest of mild or severe intensity. Four of the TEAEs leading to study drug d/c were serious: two were reported in study 003, one in a 56 year old female, another in a 62 year old white male; the third serious AE leading to study d/c was reported in study 004 in a 65 year old white male; the fourth serious AE leading to study d/c was reported in study 004 in a 63 year old white male. Further details are listed below.

Subject 004-20, who was in the 3 g Epanova group, was withdrawn from the study because of the continued need for Plavix, a prohibited medication.

Subject 105-028, who was also in the 3 g Epanova group, discontinued the study drug due to angina pectoris.

Subject 031-007, who was in the Epanova 4g group, had a TEAE of coronary artery disease.

Subject 092-015, who was in the Epanova 2g group, had a TEAE of worsening of osteoarthritis.

Reviewer's note: An important conclusion drawn from the above table is that the largest proportion of TEAEs leading to study drug d/c was reported in subjects taking Epanova.

Pool B: Subjects with Crohn's disease

Table 23: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation in > 1% by System Organ Class and Preferred Term in Pool B (Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

System Organ Class Preferred Term	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any TEAE leading to study drug discontinuation	155 (41.7)	166 (38.4)
Gastrointestinal disorders	144 (38.7)	155 (35.9)
Crohn's disease	125 (33.6)	110 (25.5)
Abdominal pain	21 (5.6)	31 (7.2)
Diarrhoea	8 (2.2)	23 (5.3)
Nausea	3 (0.8)	12 (2.8)
Frequent bowel movements	5 (1.3)	7 (1.6)
Vomiting	3 (0.8)	5 (1.2)
Abdominal tenderness	4 (1.1)	4 (0.9)
Haematochezia	4 (1.1)	1 (0.2)
General disorders and administration site conditions	5 (1.3)	11 (2.5)
Fatigue	3 (0.8)	6 (1.4)
Musculoskeletal and connective tissue disorders	6 (1.6)	10 (2.3)
Arthralgia	2 (0.5)	7 (1.6)
Metabolism and nutrition disorders	0	6 (1.4)
Decreased appetite	0	5 (1.2)
Pregnancy, puerperium and perinatal conditions	4 (1.1)	2 (0.5)
Pregnancy	4 (1.1)	2 (0.5)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event Note: AEs were coded using MedDRA version 14.1. Source: Table 3.5.3.1		

Source: from Sponsor, Table 2.7.4-20, Summary of Clinical Safety.

In subjects with Crohn's disease (Pool B), the proportion of AEs leading to study drug discontinuation was very similar in the placebo vs. the Epanova group (41.7% vs. 38.4%). In Pool B, the proportion of AEs leading to study drug discontinuation was higher than in subjects with hypertriglyceridemia (Pool A) (approximately 40% vs. 4%), which is not surprising given the different subject population and underlying diseases. Similar to Pool A, also in Pool B a smaller proportion of subjects discontinued study drug due to an AE of diarrhea in the placebo group (2%, N=8) vs. the Epanova 4g dose (5%, N=23). Similarly, a smaller proportion of subjects discontinued study drug due to an AE of nausea in the placebo group (1%, N=3) vs. the Epanova 4g dose (3%, N=12).

Reviewer's note: It should be noted that in Pool B, diarrhea and nausea were also reported with a higher incidence in subjects in the Epanova groups. At the same time, diarrhea is a cardinal manifestation of Crohn's disease and nausea is observed as well in this condition. Given the potential for confounding in the picture described above, it is

hard to establish whether the GI symptoms leading to study drug d/c were due to the study drug *per se* and/or to the underlying Crohn’s disease.

Table 24 below summarizes subject disposition

Table 24: Subject Disposition in Pool B (EPIC-1, EPIC-2, and EPIC-1E)

	Placebo n (%)	Epanova 4g n (%)
Randomized ⁽¹⁾	375	433
Completed Study ⁽²⁾	165 (44.0)	146 (33.7)
Discontinued Study	207 (55.2)	286 (66.1)
Never Dosed	3 (0.8)	1 (0.2)
Safety Population ⁽³⁾	372	432
Completed EPIC-1/2/3	165 (44.4)	146 (33.8)
Discontinuation from Study	207 (55.6)	286 (66.2)
CDAI >= 150 And Increase > 70 Points	116 (31.2)	92 (21.3)
Required Prohibitive Therapy For CD	40 (10.8)	47 (10.9)
Required Surgery For CD	1 (0.3)	2 (0.5)
Adverse Events	14 (3.8)	34 (7.9)
Withdrawal by Subject	11 (3.0)	16 (3.7)
Non-compliance	6 (1.6)	11 (2.5)
Major Protocol Violation	2 (0.5)	3 (0.7)
Pregnancy	3 (0.8)	1 (0.2)
Investigator's Decision	0	2 (0.5)
Lost to Follow-up	8 (2.2)	3 (0.7)
Other	6 (1.6)	75 (17.4)

Source: from Sponsor, Table 1.1.3.1, Integrated Summary of Safety

In Pool B, 61% (493/808) of subjects discontinued from study. The most common reasons for discontinuation were: a) worsening of CD, defined as a change on the CDAI score, observed in 26% (208/808) of the subjects; b) required prohibited medications for CD, reported in 11% (87/808) of the sample and; c) premature withdrawal due to a business decision to terminate the study, reported in 8% (66/808) of subjects.

Reviewer note: The discontinuation rate was high. Because of the discontinuation rate, and the fact that it appeared related to the severity of CD as disease, as well to the administrative decision taken by the Sponsor to terminate of the Crohn’s program, two different reasons in nature, the amount of information that can be derived from these studies on the safety profile of Epanova is somewhat limited.

Pool C: Subjects with Crohn’s disease, Long-Term Exposure

Table 25: Subject Disposition in Pool C (Long term exposure to Epanova from EPIC-1, EPIC-2, and EPIC-1E)

	Epanova 4g n (%)
Randomized ⁽¹⁾	193
Completed Study ⁽²⁾	113 (58.5)
Discontinued Study	80 (41.5)
Never Dosed	0
Safety Population ⁽³⁾	193
Discontinuation from Study	80 (41.5)
CDAI >= 150 And Increase > 70 Points	1 (0.5)
Required Prohibitive Therapy For CD	3 (1.6)
Adverse Events	7 (3.6)
Non-compliance	0
Pregnancy	0
Withdrawal by Subject	3 (1.6)
Lost to Follow-up	1 (0.5)
Other	65 (33.7)

⁽¹⁾ Percentages in this section are based on the number of subjects randomized in each integrated analysis set.

⁽²⁾ Number of subjects who completed study are based on the data collected by the CRF page of Study Completion.

⁽³⁾ Percentages under this section are based on the number of subjects in the safety population in each integrated analysis set.

Source: from Sponsor, Table 1.1.4.1, Integrated Summary of Safety

In Pool C, 41% (80/193) of subjects discontinued from study, also a quite high discontinuation rate. The most common reason for discontinuation was listed as “other”: the EPIC-1E study was terminated early, on 26 Mar 2007. Most subjects withdrew because “sponsor terminated the study”.

7.3.4 Significant Adverse Events

Please see the following Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

Under this section, this reviewer listed the AEs of primary concerns, as identified by the Sponsor as adverse events of special interest for Epanova based on the known safety profile of the drug. These included: A) bleeding and hemorrhagic AEs; B) gastrointestinal AEs; C) hyperglycemia AEs.

Reviewer’s note: This reviewer finds the identification of the primary concerns as reasonable, based on the pharmacological and safety profile of other drugs in class.

A) Bleeding and Hemorrhagic AEs

Adverse events potentially due to hemorrhage were identified by the Sponsor using the narrow and broad Standardized MedDRA Query (SMQ) for hemorrhage. In this section, all AE preferred terms identified using this SMQ are referred to as “adverse events potentially due to hemorrhage,” without further clinical assessment of the likelihood that a hemorrhagic event actually occurred.

Pool A: Subjects with Hypertriglyceridemia

Table 26 lists the adverse events potentially due to hemorrhage for Pool A.

Table 26: Treatment-Emergent Adverse Event of Special Interest: Hemorrhage by System Organ Class and Preferred terms in Pool A (Studies OM-EPA 003 and OM-EPA-004)

System Organ Class Preferred Term	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n (%)	EPANOVA (N = 300) n (%)	Olive Oil (N = 215) n (%)	EPANOVA (N = 431) n (%)	Olive Oil (N = 314) n (%)	EPANOVA (N = 731) n (%)
Any hemorrhage	0	6 (2.0)	3 (1.4)	3 (0.7)	3 (1.0)	9 (1.2)
Investigations	0	4 (1.3)	0	1 (0.2)	0	5 (0.7)
Haematocrit decreased	0	1 (0.3)	0	1 (0.2)	0	2 (0.3)
Haemoglobin decreased	0	1 (0.3)	0	1 (0.2)	0	2 (0.3)
Activated partial thromboplastin time prolonged	0	1 (0.3)	0	0	0	1 (0.1)
International normalized ratio increased	0	1 (0.3)	0	0	0	1 (0.1)
Occult blood positive	0	1 (0.3)	0	0	0	1 (0.1)
Gastrointestinal disorders	0	0	0	1 (0.2)	0	1 (0.1)
Haemorrhoidal haemorrhage	0	0	0	1 (0.2)	0	1 (0.1)
Injury, poisoning and procedural complications	0	1 (0.3)	2 (0.9)	0	2 (0.6)	1 (0.1)
Contusion	0	1 (0.3)	1 (0.5)	0	1 (0.3)	1 (0.1)
Wound haemorrhage	0	0	1 (0.5)	0	1 (0.3)	0
Renal and urinary disorders	0	0	1 (0.5)	1 (0.2)	1 (0.3)	1 (0.1)
Haematuria	0	0	1 (0.5)	1 (0.2)	1 (0.3)	1 (0.1)
Reproductive system and breast disorders	0	1 (0.3)	0	0	0	1 (0.1)
Menorrhagia	0	1 (0.3)	0	0	0	1 (0.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
 Note: AEs were classified according to System Organ Class and Preferred Term using MedDRA version 14.1.
 Source: [Table 3.12.1.1](#)

Source: from Sponsor, Table 2.7.4-21, Summary of Clinical Safety.

A total of 1.1% (12/1045) subjects experienced adverse events potentially due to hemorrhage in Pool A. The adverse events potentially due to hemorrhage were reported in five different SOCs: five subjects (all in the Epanova groups) were listed under “Investigations” for five preferred terms. The remaining four subjects were listed under the following SOCs: gastrointestinal disorders, injury, poisoning and procedural complications, renal and urinary disorders, and reproductive system and breast disorders. Of these 12 subjects, six were reported in study 003, and six were reported in study 004. The percent of subjects with adverse events potentially due to hemorrhage was not different in the olive oil group vs. the Epanova group. Of note, the activated

partial thromboplastin time (sec) and the prothrombin time (sec) were defined as low 23.3, high 32.1 and low 9.2, high 11.6, respectively.

Reviewer’s note: based on the limited number of events reported, the background prevalence of adverse events potentially due to hemorrhage in Pool A appeared not increased and the number of subjects with adverse events potentially due to hemorrhage not different in the olive oil vs. the Epanova group.

Pool B: Subjects with Crohn’s disease

Table 27: Treatment-Emergent Adverse Event of Special Interest: Hemorrhage Occurring in >1 Subject by System Organ Class and Preferred Terms in Pool B (Studies EPIC-1, EPIC-2, and EPIC-1E)

System Organ Class Preferred Term	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any hemorrhage	31 (8.3)	37 (8.6)
Gastrointestinal disorders	23 (6.2)	29 (6.7)
Rectal haemorrhage	10 (2.7)	12 (2.8)
Haematochezia	12 (3.2)	11 (2.5)
Haemorrhoidal haemorrhage	1 (0.3)	2 (0.5)
Skin and subcutaneous tissue disorders	1 (0.3)	3 (0.7)
Ecchymosis	0	2 (0.5)
Reproductive system and breast disorders	2 (0.5)	2 (0.5)
Menorrhagia	2 (0.5)	0
Respiratory, thoracic and mediastinal disorders	1 (0.3)	2 (0.5)
Epistaxis	1 (0.3)	2 (0.5)
Renal and urinary disorders	3 (0.8)	1 (0.2)
Haematuria	3 (0.8)	1 (0.2)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Note: AEs were coded using MedDRA version 14.1. Source: Table 3.12.3.1		

Source: from Sponsor, Table 2.7.4-22, Summary of Clinical Safety.

Approximately 8% of subjects (68/804) experienced any adverse events potentially due to hemorrhage in Pool B. The adverse events potentially due to hemorrhage were reported in five different SOCs: gastrointestinal disorders, skin and subcutaneous tissue disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders, and renal and urinary disorders.

Reviewer’s note: A similar proportion (approximately 8%) of any adverse events potentially due to hemorrhage was observed in the placebo and Epanova 4g groups. Most of these events were of gastrointestinal nature, which is consistent with the nature of Crohn’s disease.

Pool C: Subjects with Crohn’s disease, Long-Term Exposure

Table 28 Treatment Emergent Adverse Event of Special Interest: Hemorrhage by System Organ Class and Preferred Terms in Pool C: Long Term Exposure from EPIC-1, EPIC-2, EPIC-3 and EPIC-1E

System Organ Class Preferred Term	Epanova 4g (N=193) n (%)
Any Hemorrhage	19 (9.8)
GASTROINTESTINAL DISORDERS	15 (7.8)
HAEMATOCHEZIA	8 (4.1)
RECTAL HAEMORRHAGE	5 (2.6)
DIARRHOEA HAEMORRHAGIC	1 (0.5)
GINGIVAL BLEEDING	1 (0.5)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (1.0)
METRORRHAGIA	1 (0.5)
UTERINE HAEMORRHAGE	1 (0.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (1.0)
EPISTAXIS	2 (1.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1.0)
ECCHYMOSIS	1 (0.5)
INCREASED TENDENCY TO BRUISE	1 (0.5)

Source: from Sponsor, Table 3.12.4.1, Integrated Summary of Safety

Approximately 10% of subjects (19/193) experienced any adverse events potentially due to hemorrhage in Pool C. The adverse events potentially due to hemorrhage were reported in four different SOCs: gastrointestinal disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders, and skin and subcutaneous tissue disorders.

B) Gastrointestinal AEs

Adverse events potentially due to gastrointestinal TEAEs were identified by the Sponsor using the narrow and broad SMQ for gastrointestinal events.

Pool A: Subjects with Hypertriglyceridemia

**Table 29: Treatment-Emergent Adverse Events of Special Interest:
Gastrointestinal Events by System Organ Class and Preferred Terms in Pool A
(Studies OM-EPA-003 and OM-EPA-004)**

Clinical Review – Safety
 Giovanni Cizza, MD, PhD, MHSc
 NDA 205060
 EPANOVA (omega-3-carboxylic acids)

System Organ Class Preferred Term	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n (%)	EPANOVA (N = 300) n (%)	Olive Oil (N = 215) n (%)	EPANOVA (N = 431) n (%)	Olive Oil (N = 314) n (%)	EPANOVA (N = 731) n (%)
Any gastrointestinal AE	6 (6.1)	65 (21.7)	17 (7.9)	83 (19.3)	23 (7.3)	148 (20.2)
Gastrointestinal disorders	6 (6.1)	65 (21.7)	17 (7.9)	83 (19.3)	23 (7.3)	148 (20.2)
Diarrhoea	2 (2.0)	25 (8.3)	5 (2.3)	49 (11.4)	7 (2.2)	74 (10.1)
Nausea	1 (1.0)	19 (6.3)	3 (1.4)	19 (4.4)	4 (1.3)	38 (5.2)
Eructation	1 (1.0)	11 (3.7)	0	12 (2.8)	1 (0.3)	23 (3.1)
Abdominal pain	3 (3.0)	6 (2.0)	3 (1.4)	8 (1.9)	6 (1.9)	14 (1.9)
Vomiting	1 (1.0)	6 (2.0)	0	8 (1.9)	1 (0.3)	14 (1.9)
Dyspepsia	0	5 (1.7)	3 (1.4)	5 (1.2)	3 (1.0)	10 (1.4)
Flatulence	0	1 (0.3)	0	9 (2.1)	0	10 (1.4)
Abdominal pain upper	1 (1.0)	6 (2.0)	0	3 (0.7)	1 (0.3)	9 (1.2)
Constipation	0	2 (0.7)	3 (1.4)	5 (1.2)	3 (1.0)	7 (1.0)
Abdominal discomfort	0	0	0	5 (1.2)	0	5 (0.7)
Abdominal distension	0	0	0	4 (0.9)	0	4 (0.5)
Regurgitation	0	4 (1.3)	0	0	0	4 (0.5)
Gastritis	0	1 (0.3)	0	2 (0.5)	0	3 (0.4)
Abdominal tenderness	0	1 (0.3)	0	0	0	1 (0.1)
Defaecation urgency	0	1 (0.3)	0	0	0	1 (0.1)
Diverticulum intestinal	0	1 (0.3)	0	0	0	1 (0.1)
Gastroduodenitis	0	1 (0.3)	0	0	0	1 (0.1)
Gastrointestinal hypermotility	0	1 (0.3)	0	0	0	1 (0.1)
Gastroesophageal reflux disease	1 (1.0)	0	0	1 (0.2)	1 (0.3)	1 (0.1)
Oesophageal pain	0	1 (0.3)	0	0	0	1 (0.1)
Abnormal faeces	0	0	1 (0.5)	0	1 (0.3)	0
Faecal volume increased	0	0	1 (0.5)	0	1 (0.3)	0
General disorders and administration site conditions	0	2 (0.7)	0	0	0	2 (0.3)
Chest pain	0	1 (0.3)	0	0	0	1 (0.1)
Non-cardiac chest pain	0	1 (0.3)	0	0	0	1 (0.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
 Note: AEs were classified according to System Organ Class and Preferred Term using MedDRA version 14.1.
 Source: [Table 3.13.1.1](#)

Source: from Sponsor, Table 2.7.4-23, Summary of Clinical Safety.

In Pool A, approximately 16% (171/1045) of subjects experienced any gastrointestinal TEAEs. The most common AEs were diarrhea, nausea, and eructation. Diarrhea and nausea were five-fold, and eructation was three-fold more common in the Epanova

group vs. the olive-oil group. The incidence of any gastrointestinal TEAEs was similar in study 003, approximately 18% (71/399) and in study 004, approximately 15% (100/646).

Reviewer’s note: The incidence of gastrointestinal TEAEs was clearly and consistently higher in the Epanova group.

Table 30 lists the gastrointestinal TEAEs by dose level.

Table 30: Treatment-Emergent Adverse Events of Special Interest: Gastrointestinal Events Occurring in >1 Subject in Epanova Total Dose Group by System Organ Class and Preferred Terms in Pool A (Studies OM-EPA-003 and OM-EPA-004)

System Organ Class Preferred Term	Olive Oil (N = 314) n (%)	EPANOVA 2 g (N = 315) n (%)	EPANOVA 3 g (N = 101) n (%)	EPANOVA 4 g (N = 315) n (%)
Any gastrointestinal AE	23 (7.3)	46 (14.6)	20 (19.8)	82 (26.0)
Gastrointestinal disorders	23 (7.3)	46 (14.6)	20 (19.8)	82 (26.0)
Diarrhoea	7 (2.2)	23 (7.3)	5 (5.0)	46 (14.6)
Nausea	4 (1.3)	12 (3.8)	8 (7.9)	18 (5.7)
Eructation	1 (0.3)	9 (2.9)	4 (4.0)	10 (3.2)
Abdominal pain	6 (1.9)	6 (1.9)	1 (1.0)	7 (2.2)
Flatulence	0	3 (1.0)	1 (1.0)	6 (1.9)
Dyspepsia	3 (1.0)	4 (1.3)	1 (1.0)	5 (1.6)
Abdominal discomfort	0	1 (0.3)	0	4 (1.3)
Abdominal pain upper	1 (0.3)	4 (1.3)	1 (1.0)	4 (1.3)
Constipation	3 (1.0)	2 (0.6)	1 (1.0)	4 (1.3)
Vomiting	1 (0.3)	6 (1.9)	4 (4.0)	4 (1.3)
Abdominal distension	0	2 (0.6)	0	2 (0.6)
Regurgitation	0	0	2 (2.0)	2 (0.6)
Gastritis	0	1 (0.3)	1 (1.0)	1 (0.3)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Note: AEs were coded using MedDRA version 14.1. Source: Table 3.13.2.1				

Source: Table 2.7.4-24, Summary of Clinical Safety.

The incidence of any gastrointestinal TEAEs was 7.3% in the olive oil group, 14.6% in the Epanova 2g group, 19.8% in the Epanova 3g group, and 26% in the Epanova 4g group. Diarrhea, nausea and eructation were the three most common terms. Diarrhea

and flatulence were approximately twice more common in the Epanova 4g vs. the Epanova 2g (diarrhea: 14.6% vs. 7.3%; flatulence: 1.9% vs. 1.0%).

Reviewer’s note: the incidence of any gastrointestinal TEAEs appeared to increase progressively from olive oil with increasing doses of Epanova. The incidence of specific gastrointestinal TEAEs was clearly higher in Epanova 4g than in Epanova 2g.

Table 31: Treatment-Emergent Adverse Events of Special Interest: Subjects reporting a TEAEs of abdominal pain, abdominal pain upper, or abdominal discomfort in Pool A (Studies OM-EPA-003 and OM-EPA-004)

	Olive oil N=314	Epanova 2g N=315	Epanova 3g N=101	Epanova 4g N=315	Epanova all doses N=731
Abdominal pain	6	6	1	7	14
Abdominal pain upper	1	4	1	4	9
Abdominal discomfort	0	1	0	4	5
Total	7 (2.2%)	11 (3.5%)	2 (2.0%)	15 (4.7%)	28 (3.8%)

Source: created by reviewer based on the Integrated Summary of Safety. Each subject is represented once in the column totals.

The percent of subjects reporting the combined terms of “abdominal pain” depicted above was greater in the Epanova all doses group than in the olive oil group (3.8% vs. 2.2%). Within the three different doses of Epanova the lowest percent of subjects reporting the combined terms of “abdominal pain” was observed at the Epanova 3g dose and the highest percent at the Epanova 4g dose.

Reviewer’s note: the percent of reporting the combined terms of “abdominal pain” was greater in the Epanova group vs. the Olive group with no clear pattern for a dose-response among different doses of Epanova.

Pool B: Subjects with Crohn’s disease

Table 32 depicts the gastrointestinal TEAEs in Pool B.

Table 32: Treatment-Emergent Adverse Events of Special Interest: Gastrointestinal Events Occurring in >1 Subject by System Organ Class and Preferred Term in Pool B (Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

System Organ Class Preferred Term	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any gastrointestinal AE	182 (48.9)	238 (55.1)
Gastrointestinal disorders	181 (48.7)	238 (55.1)
Abdominal pain	83 (22.3)	118 (27.3)
Diarrhoea	48 (12.9)	87 (20.1)
Nausea	23 (6.2)	53 (12.3)
Abdominal tenderness	31 (8.3)	36 (8.3)
Abdominal distension	17 (4.6)	27 (6.3)
Flatulence	25 (6.7)	24 (5.6)
Dyspepsia	18 (4.8)	23 (5.3)
Vomiting	13 (3.5)	22 (5.1)
Constipation	11 (3.0)	21 (4.9)
Frequent bowel movements	12 (3.2)	19 (4.4)
Abdominal pain upper	15 (4.0)	17 (3.9)
Gastroesophageal reflux disease	7 (1.9)	11 (2.5)
Abdominal discomfort	3 (0.8)	8 (1.9)
Eructation	0	8 (1.9)
Abdominal pain lower	4 (1.1)	6 (1.4)
Anorectal discomfort	0	4 (0.9)
Breath odour	0	4 (0.9)
Gastrointestinal sounds abnormal	3 (0.8)	4 (0.9)
Anal inflammation	0	3 (0.7)
Defaecation urgency	2 (0.5)	3 (0.7)
Gastritis	1 (0.3)	3 (0.7)
Gastrointestinal pain	6 (1.6)	2 (0.5)
General disorders and administration site conditions	4 (1.1)	1 (0.2)
Chest pain	2 (0.5)	1 (0.2)
Non-cardiac chest pain	3 (0.8)	0

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
 Note: AEs were coded using MedDRA version 14.1.
 Source: [Table 3.13.3.1](#)

Source: from Sponsor, Table 2.7.4-25, Summary of Clinical Safety.

In Pool B, approximately 52% of subjects (420/804) experienced any gastro-intestinal TEAEs. In addition to abdominal pain described in greater detail in table, the most common terms reported were, diarrhea and nausea. These terms were twice less common in the placebo group (diarrhea 12.9% vs. 20.1%; nausea: 6.2% vs. 12.3%).

To further characterize the gastrointestinal TEAEs, this reviewer combined the following terms listed in Table 33, as they are virtually indistinguishable from a clinical perspective.

Table 33: Combination of the Different Preferred Terms Indicating “Abdominal Pain”

	Placebo (N=372) N (%)	Epanova 4g (N=432) N (%)
Abdominal pain	83 (22.3%)	118 (27.3%)
Abdominal tenderness	31 (8.3%)	36 (8.3%)
Abdominal pain upper	15 (4.0%)	17 (3.9%)
Abdominal discomfort	3(0.8%)	8 (1.9%)
Abdominal pain lower	4 (1.1%)	6 (1.4%)
Gastrointestinal pain	6 (1.6%)	2 (0.5%)

Source: created by reviewer based on Table 2.7.4-25 of the Summary of Clinical Safety.

The preferred terms abdominal pain, abdominal discomfort, and gastrointestinal pain were more common in the Epanova 4g group than in the placebo group.

Reviewer’s note: The high background prevalence, 52% of subjects with Crohn’s disease having gastrointestinal TEAEs, was not surprising given the nature of this condition. In spite of the high background prevalence of gastrointestinal symptoms in subjects with Crohn’s, when the equivalent terms indicating abdominal pain were considered collectively, it appeared clear that, similar to Pool A, also in this population of subjects with Crohn’s disease Epanova 4g was associated with more terms referring to abdominal pain (as well as diarrhea and nausea) than placebo.

Pool C: Subjects with Crohn’s disease, Long-Term Exposure

Table 34 depicts the gastrointestinal TEAEs in Pool C.

Table 34: Treatment Emergent Adverse Events of Special Interest: Gastrointestinal Events by System Organ Class and Preferred Terms Pool C: Long Term Exposure from EPIC-1, EPIC 2, EPIC-3, and EPIC-1E

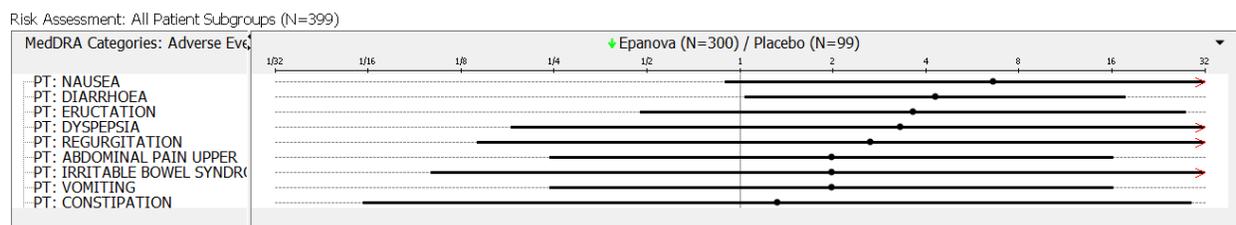
System Organ Class Preferred Term	Epanova 4g (N=193) n (%)
Any Gastrointestinal AE	108 (56.0)
GASTROINTESTINAL DISORDERS	108 (56.0)
ABDOMINAL PAIN	60 (31.1)
DIARRHOEA	43 (22.3)
ABDOMINAL TENDERNESS	21 (10.9)
NAUSEA	20 (10.4)
ABDOMINAL DISTENSION	14 (7.3)
DYSPEPSIA	14 (7.3)
FLATULENCE	13 (6.7)
VOMITING	13 (6.7)
CONSTIPATION	12 (6.2)
ABDOMINAL PAIN UPPER	10 (5.2)
FREQUENT BOWEL MOVEMENTS	9 (4.7)
GASTROESOPHAGEAL REFLUX DISEASE	9 (4.7)
ABDOMINAL DISCOMFORT	5 (2.6)
ERUCTATION	5 (2.6)
ABDOMINAL PAIN LOWER	4 (2.1)

Adverse Event Coding Dictionary: MedDRA 14.1; Preferred Terms included are results of both narrow and broad queries using the Standard MedDRA Query of Gastrointestinal Events.
 Percentages are based on the number of subjects in the safety population in each integrated analysis set.
 An adverse event is considered to be treatment emergent if the event started on or after the date of administration of the first dose of study drug.
 A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

The gastrointestinal TEAEs reported in Pool C were typical of the underlying disease, Crohn’s disease. The lack of a control group prevents any further conclusion.

Figure 1 depicts the relative risk (RR) of gastrointestinal TEAEs for study 003, 004 and 003 and 004 combined.

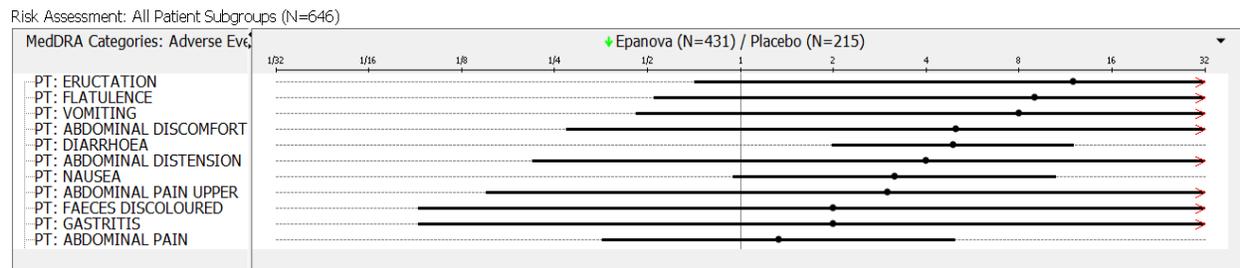
Figure 1: Relative Risk (RR) for Gastrointestinal TEAEs in Subjects with Epanova vs. Olive Oil, Study 003



In 003, the RR for a TEAE of diarrhea was 4.29 (95% CI 1.03 to 17.75) and the RR for a TEAE of nausea was 6.6 (95% CI 0.89 to 48.54) in subjects on EPANOVA.

Figure 2: Relative Risk (RR) for Gastrointestinal TEAEs in Subjects with Epanova vs. Olive Oil, Study 004

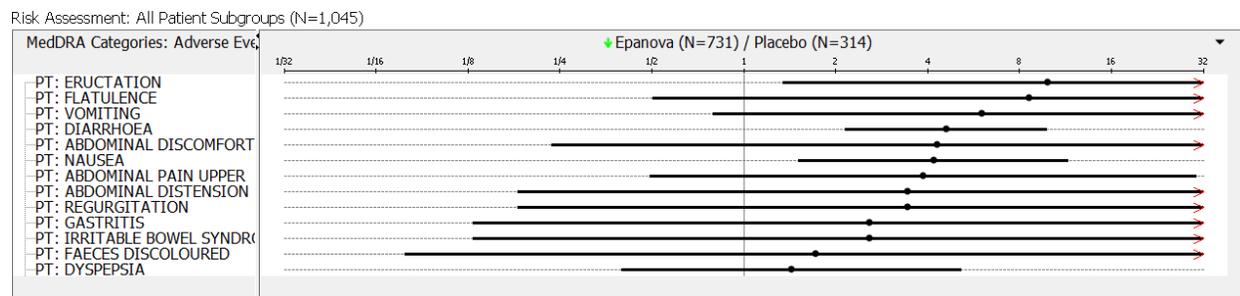
Fig. 2 shows the RR for the GI TEAEs in study 004



Source: created by reviewer in J review.

Figure 3: Relative Risk (RR) for Gastrointestinal TEAEs in Subjects with Epanova vs. Olive Oil, Study 003 and Study 004 Pooled Together

Fig. 3 shows the RR for the GI TEAEs for study 003 and study 004 pooled together.



Source: created by reviewer in J review.

As depicted in Fig. 3, the RR for a TEAE of the following GI TEAEs was the following (Epanova Group vs. the OLIVE OIL Group)

- Eructation: RR 9.87; 95% CI 1.34 to 72.82
- Diarrhea: RR 4.60; 95% CI 2.14 to 9.87
- Nausea: RR 4.18; 95% CI 1.50 to 11.62.

In addition, in exploratory analyses of gastrointestinal RR sub-categorized by use of statin, diagnosis of diabetes, age, sex, race, and ethnicity there was no excess of RR in subjects taking Epanova (data not shown).

Reviewer's note: The analysis of RR depicted above should be considered exploratory with all its inherent biases and should be interpreted in the general context of this dataset.

C) Hyperglycemia AEs

Adverse events potentially attributable to hyperglycemia TEAEs were identified by the Sponsor using the narrow and broad SMQ for hyperglycemia. In this section, all AE preferred terms identified using this SMQ are referred to as “preferred terms potentially related to hyperglycemia,” without further clinical assessment.

Pool A: Subjects with Hypertriglyceridemia

Table 35: Treatment-Emergent Adverse Event of Special Interest: Hyperglycemia by System Organ Class and Preferred terms in Pool A (Studies OM-EPA 003 and OM-EPA-004)

System Organ Class Preferred Term	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n (%)	EPANOVA (N = 300) n (%)	Olive Oil (N = 215) n (%)	EPANOVA (N = 431) n (%)	Olive Oil (N = 314) n (%)	EPANOVA (N = 731) n (%)
Any hyperglycemia	5 (5.1)	11 (3.7)	5 (2.3)	11 (2.6)	10 (3.2)	22 (3.0)
Metabolism and nutrition disorders	2 (2.0)	4 (1.3)	4 (1.9)	8 (1.9)	6 (1.9)	12 (1.6)
Diabetes mellitus	1 (1.0)	3 (1.0)	3 (1.4)	4 (0.9)	4 (1.3)	7 (1.0)
Type 2 diabetes mellitus	0	1 (0.3)	0	1 (0.2)	0	2 (0.3)
Diabetes mellitus inadequate control	0	0	0	1 (0.2)	0	1 (0.1)
Hyperglycaemia	0	0	1 (0.5)	1 (0.2)	1 (0.3)	1 (0.1)
Increased appetite	0	0	0	1 (0.2)	0	1 (0.1)
Hyperlipidaemia	1 (1.0)	0	0	0	1 (0.3)	0
Investigations	3 (3.0)	8 (2.7)	1 (0.5)	3 (0.7)	4 (1.3)	11 (1.5)
Blood glucose increased	0	3 (1.0)	1 (0.5)	1 (0.2)	1 (0.3)	4 (0.5)
Weight increased	0	3 (1.0)	0	1 (0.2)	0	4 (0.5)
Glycosylated haemoglobin increased	0	2 (0.7)	0	1 (0.2)	0	3 (0.4)
Weight decreased	0	1 (0.3)	0	0	0	1 (0.1)
Blood triglycerides increased	3 (3.0)	0	0	0	3 (1.0)	0
Renal and urinary disorders	0	1 (0.3)	0	0	0	1 (0.1)
Glycosuria	0	1 (0.3)	0	0	0	1 (0.1)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
 Note: AEs were classified according to System Organ Class and Preferred Term using MedDRA version 14.1.
 Source: [Table 3.14.1.1](#)

Source: from Sponsor, Table 2.7.4-26, Summary of Clinical Safety.

Reviewer’s note: When analyzing the individual preferred terms, the overall percentage of subjects with any preferred terms potentially related to hyperglycemia was not different in Epanova groups vs. the olive oil group.

To further explore this issue of potential clinical importance, this reviewer combined under “diabetes mellitus” the terms listed in Table 36, as they are virtually indistinguishable from a clinical point.

Table 36: Combination of the Different Preferred Terms Indicating “Diabetes Mellitus” in Pool A

	Olive Oil (N=314) N (%)	Epanova (N=731) N (%)
Diabetes mellitus	4 (1.3)	7 (1.0)
Type 2 diabetes Mellitus	0	2 (0.3)
Diabetes mellitus inadequate control	0	1 (0.1)
Hyperglycaemia	1 (0.3)	1 (0.1)
Blood glucose Increased	1 (0.3)	4 (0.5)
Glycosylated haemoglobin increased	0	3 (0.4)
Glycosuria	0	1 (0.1)

Source: created by reviewer based on Table 2.7.4-25 of the Summary of Clinical Safety.

The incidence of preferred terms potentially related to diabetes mellitus, approximately 2%, was not different in the olive oil vs. the Epanova group.

Reviewer’s note: Even when the relevant preferred terms were combined there did not appear to be an increased incidence of terms potentially related to diabetes mellitus in the pooled Epanova group.

To address the question whether any specific dose of Epanova was associated with “diabetes mellitus” this reviewer examined also the doses of Epanova, as depicted in Table 37 by the applicant.

Table 37: Treatment-Emergent Adverse Event of Special Interest: Hyperglycemia by Dose Level, System Organ Class and Preferred terms in Pool A (Studies OM-EPA 003 and OM-EPA-004)

System Organ Class Preferred Term	Olive Oil (N=314) n (%)	Epanova 2g (N=315) n (%)	Epanova 3g (N=101) n (%)	Epanova 4g (N=315) n (%)
Any Hyperglycemia	10 (3.2)	8 (2.5)	3 (3.0)	11 (3.5)
METABOLISM AND NUTRITION DISORDERS	6 (1.9)	3 (1.0)	1 (1.0)	8 (2.5)
DIABETES MELLITUS	4 (1.3)	0	0	7 (2.2)
DIABETES MELLITUS INADEQUATE CONTROL	0	0	0	1 (0.3)
HYPERGLYCAEMIA	1 (0.3)	1 (0.3)	0	0
HYPERLIPIDAEMIA	1 (0.3)	0	0	0
INCREASED APPETITE	0	1 (0.3)	0	0
TYPE 2 DIABETES MELLITUS	0	1 (0.3)	1 (1.0)	0
INVESTIGATIONS	4 (1.3)	5 (1.6)	3 (3.0)	3 (1.0)
BLOOD GLUCOSE INCREASED	1 (0.3)	1 (0.3)	1 (1.0)	2 (0.6)
GLYCOSYLATED HAEMOGLOBIN INCREASED	0	2 (0.6)	0	1 (0.3)
WEIGHT INCREASED	0	2 (0.6)	1 (1.0)	1 (0.3)
BLOOD TRIGLYCERIDES INCREASED	3 (1.0)	0	0	0
WEIGHT DECREASED	0	0	1 (1.0)	0

Adverse Event Coding Dictionary: MedDRA 14.1; Preferred Terms included are results of both narrow and broad queries using the Standard MedDRA Query of Hyperglycemia.
 Percentages are based on the number of subjects in the safety population in each integrated analysis set.
 An adverse event is considered to be treatment emergent if the event started on or after the date of administration of the first dose of study drug.
 A subject with two or more adverse events in the same system organ class (or with the same preferred term) is counted only once for that system organ class (or preferred term).

Source: from Sponsor, Table 3.14.2.1, Integrated Summary of Safety.

Table 38: Combined Preferred Terms for “Diabetes Mellitus”

	Olive Oil (N=314) n (%)	Epanova 2g (N=315) n (%)	Epanova 3g (N=101) n (%)	Epanova 4g (N=315) n (%)
Diabetes mellitus	4 (1.3)	0	0	7 (2.2)
Diabetes mellitus inadequate control	0	0	0	1 (0.3)
Hyperglycemia	1 (0.3)	1 (0.3)	0	0
Type 2 diabetes mellitus	0	1 (0.3)	1 (1.0)	0
Blood glucose increased	1 (0.3)	1 (0.3)	1 (1.0)	2 (0.6)
Glycosylated hemoglobin increased	0	2 (0.6)	0	1 (0.3)
Total	6 (1.9)	5 (1.6)	2 (2.0)	11 (3.5)

Source: created by reviewer based on Table 3.14.2.1 of the Integrated Summary of Safety.

The proportion of subjects with preferred terms suggestive of type 2 diabetes was similar to the olive oil group in the Epanova 2g and in the Epanova 3g; in the Epanova 4g it was two-fold greater.

Reviewer’s note: Even with the caveat of the small absolute number of cases, the possibility that Epanova 4g may be associated with more preferred terms suggestive of type 2 diabetes cannot be ruled out. Additional analyses were therefore requested to

the Sponsor in reference to changes in central tendency for glucose and HbA1c from baseline by diabetes status.

Study 003

Table 39 depicts the TEAEs potentially representing worsening of diabetes.

Table 39: Treatment Emergent Adverse Events Representing Worsening of Diabetes by Dose Level, System Organ Class and Preferred Term — Safety Population from OM-EPA-003

System Organ Class Preferred Term	Olive Oil N=99 n (%)	Epanova 2 g N=100 n (%)	Epanova 3 g N=101 n (%)	Epanova 4 g N=99 n (%)
Subjects with Any Treatment-Emergent Adverse Event (TEAE) [1]	1 (1.0%)	1 (1.0%)	2 (2.0%)	5 (5.1%)
Total of TEAEs	1	1	3	6
Investigations	0 (0.0%)	1 (1.0%)	1 (1.0%)	2 (2.0%)
Blood glucose increased	0 (0.0%)	0 (0.0%)	1 (1.0%)	2 (2.0%)
Glycosylated haemoglobin increased	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (1.0%)
Metabolism and nutrition disorders	1 (1.0%)	0 (0.0%)	1 (1.0%)	3 (3.0%)
Diabetes mellitus	1 (1.0%)	0 (0.0%)	0 (0.0%)	3 (3.0%)
Type 2 diabetes mellitus	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Renal and urinary disorders	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Glycosuria	0 (0.0%)	0 (0.0%)	1 (1.0%)	0 (0.0%)

Source: from Sponsor, Table 1.11.2-1. of the 1.11.2 Safety Information Amendment

The number and percent of subjects reporting a TEAEs was as follows: 1 (1.0%), 1 (1.0%), 2 (2.0%) and 5 (5.1%) in the olive oil group, Epanova 2g Group, Epanova 3g, and Epanova 4g group, respectively.

Table 40 depicts baseline and end of treatment blood glucose by treatment group and diabetes status

Table 40: Baseline and End of Treatment Blood Glucose by Treatment Group and Diabetes Status — Safety Population from OM-EPA-003

Blood Glucose (mg/dL)	Olive Oil N=99	Epanova 2g N=100	Epanova 3g N=101	Epanova 4g N=99
Without Diabetes, Baseline N	68	62	56	61
Mean (SD)	102.5 (13.33)	104.3 (14.48)	104.3 (16.36)	101.5 (13.31)
Median	100.50	101.00	101.50	99.00
Min, Max	81.0, 155.0	78.0, 149.0	75.0, 171.0	79.0, 140.0
Without Diabetes End of Treatment N	62	59	47	57
Mean (SD)	102.9 (16.59)	104.1 (16.35)	107.0 (13.78)	105.4 (15.89)
Median	98.50	101.00	105.00	103.00
Min, Max	75.0, 177.0	74.0, 174.0	83.0, 141.0	79.0, 173.0
With Diabetes, Baseline N	31	38	45	37
Mean (SD)	148.0 (47.16)	149.7 (51.09)	149.6 (28.48)	158.4 (47.75)
Median	153	139.50	149.00	153.00
Min, Max	81.0, 297.0	65.0, 296.0	77.0, 198.0	93.0, 267.0
With Diabetes, End of Treatment N	29	34	38	35
Mean (SD)	159.1 (50.58)	155.6 (51.30)	163.0 (49.40)	165.4 (52.97)
Median	152.0	152.50	158.50	158.00
Min, Max	80.0, 310.0	66.0, 311.0	73.0, 329.0	89.0, 283.0

Source: modified by reviewer from Table 1.11.2-3. of 1.11.2 Safety Information Amendment

In subjects without diabetes, in the olive oil group and in the Epanova 2g group there were no changes in median blood glucose between baseline and end of treatment. In the Epanova 3g group and Epanova 4g group the median change from baseline were 3 and 2 mg/dL, respectively.

In subjects with diabetes, in olive oil, Epanova 2g, Epanova 3g, and Epanova 4g,

The median change from baseline to end of treatment was 10.0, 12.00, 8.50, and 3.00 mg/dL, respectively.

Reviewer's note: median changes in fasting glucose between baseline and end of treatment were larger in subjects with diabetes vs. subjects without diabetes. This is not surprising in view of the fact that subjects with diabetes may experience changes of larger magnitude over time in fasting glucose levels vs. subjects without diabetes. It should be noted however that the arithmetical increases in mean fasting glucose and the median changes in fasting glucose observed between baseline and end of treatment in the Epanova 4g group could also be compatible with an effect of Epanova

in increasing fasting glucose levels at the highest dose. Given the small sample size and the fact that fasting glucose levels were collected only twice in the study, no definitive conclusion as to whether the changes over time observed in fasting glucose were within the normal temporal variability of this parameter or whether they were exaggerated and tended towards an increase in the Epanova 4g group can be made based on this post-hoc exploratory analysis.

Table 41 depicts baseline and end of treatment Hemoglobin A1c by treatment group and diabetes status

Table 41: Baseline and End of Treatment in Hemoglobin A1c by Treatment Group and Diabetes Status- Safety Population from OM-EPA-003

Hemoglobin A1c (%)	Olive Oil N=99	Epanova 2g N=100	Epanova 3g N=101	Epanova 4g N=99
Without Diabetes, Baseline N	68	60	56	62
Mean (SD)	5.5 (0.41)	5.6 (0.35)	5.6 (0.38)	5.5 (0.34)
Median	5.50	5.60	5.60	5.60
Min, Max	4.8, 6.4	4.4, 6.4	4.7, 6.4	4.5, 6.2
Without Diabetes End of Treatment N	61	59	46	56
Mean (SD)	5.6 (0.44)	5.7 (0.39)	5.7 (0.40)	5.6 (0.39)
Median	5.50	5.70	5.65	5.60
Min, Max	4.7, 6.8	4.4, 6.9	4.8, 6.8	4.7, 6.6
With Diabetes, Baseline N	31	38	45	37
Mean (SD)	7.1 (1.13)	6.9 (1.03)	7.2 (0.86)	7.1 (1.05)
Median	7.1	7.0	7.1	7.0
Min, Max	5.2, 8.7	5.3, 10.4	5.1, 8.9	5.1, 9.2
With Diabetes, End of Treatment N	29	34	38	34
Mean (SD)	7.3 (1.32)	7.1 (1.38)	7.3 (1.09)	7.3 (1.26)
Median	7.1	6.9	7.2	7.3
Min, Max	5.5, 10.0	5.4, 12.1	5.2, 10.8	5.1, 10.9

Source: modified by reviewer from Table 1.11.2-2. of 1.11.2 Safety Information Amendment

There were no meaningful changes between baseline and end of treatment in hemoglobin A1c both in subjects without diabetes and in subjects with diabetes.

Study 004

Table 42 depicts baseline and end of treatment blood glucose by treatment Group and diabetes status

Table 42: Baseline and End of Treatment in Blood Glucose by Treatment Group and Diabetes Status - Safety Population from OM-EPA-004

Blood Glucose (mg/dL)	Olive Oil N=100	Epanova 2g N=101	Epanova 4g N=99
Without Diabetes, Baseline N	59	57	68
Mean (SD)	101.0 (15.69)	106.3 (10.01)	106.8 (21.26)
Median	99.00	106.00	102.00
Min, Max	78.0, 175.0	81.0, 131.0	69.0, 212.0
Without Diabetes End of Treatment N	58	56	66
Mean (SD)	100.0 (10.92)	108.3 (13.41)	104.3 (15.53)
Median	98.50	107.50	101.00
Min, Max	81.0, 128.0	82.0, 160.0	80.0, 164.0
With Diabetes, Baseline N	156	158	148
Mean (SD)	146.4 (48.23)	152.7 (47.55)	145.9 (38.66)
Median	136.0	140.50	141.00
Min, Max	74.0, 430.0	69.0, 347.0	73.0, 323.0
With Diabetes, End of Treatment N	153	152	140
Mean (SD)	147.9 (52.02)	148.9 (44.32)	148.3 (46.12)
Median	136.00	140.00	139.50
Min, Max	65.0, 431.0	68.0, 303.0	62.0, 349.0

Source: modified by reviewer from Table 1.11.2-6. of 1.11.2 Safety Information Amendment

In study 004, there were no meaningful changes between baseline and end of treatment in fasting blood glucose both in subjects without diabetes and in subjects with diabetes.

Table 43 depicts baseline and end of treatment Hemoglobin A1c by treatment group and diabetes status

Table 43: Baseline and End of Treatment in Hemoglobin A1c by Treatment Group and Diabetes Status — Safety Population from OM-EPA-004

Hemoglobin A1c (%)	Olive Oil N=100	Epanova 2g N=101	Epanova 4g N=99
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Without Diabetes, Baseline N	59	57	68
Mean (SD)	5.8 (0.33)	5.9 (0.37)	5.8 (0.34)
Median	5.90	5.90	5.70
Min, Max	5.0, 6.4	5.0, 6.4	5.0, 6.4
Without Diabetes, End of Treatment N	56	54	62
Mean (SD)	5.8 (0.29)	5.8 (0.37)	5.7 (0.37)
Median	5.70	5.80	5.80
Min, Max	5.2, 6.4	5.1, 6.7	5.0, 6.8
With Diabetes, Baseline N	156	158	148
Mean (SD)	7.1 (1.06)	7.1 (1.00)	7.1 (0.95)
Median	6.90	6.90	6.90
Min, Max	5.1, 9.9	5.3, 10.0	5.4, 9.6
With Diabetes End of Treatment N	147	144	133
Mean (SD)	7.2 (1.19)	7.2 (1.14)	7.2 (1.24)
Median	6.90	7.00	6.90
Min, Max	5.1, 11.1	5.3, 10.9	5.1, 11.9

Source: modified by reviewer from Table 1.11.2-5. of 1.11.2 Safety Information Amendment

In study 004, there were no meaningful changes between baseline and end of treatment in Hemoglobin A1c both in subjects without diabetes and in subjects with diabetes.

Pool A

Table 44 depicts baseline and end of treatment blood glucose by treatment Group and diabetes status

Table 44: Baseline and Treatment in Blood Glucose by Treatment Group and Diabetes Status — Safety Population from Pool A

Blood Glucose (mg/dL)	Olive Oil N=314	Epanova 2g N=315	Epanova 3g N=101	Epanova 4g N=315
Without Diabetes, Baseline N	127	119	56	129
Mean (SD)	101.8 (14.43)	105.3 (12.52)	104.3 (16.36)	104.3 (18.07)
Median	100.00	104.00	101.50	101.00
Min, Max	78.0, 175.0	78.0, 149.0	75.0, 171.0	69.0, 212.0
Without Diabetes End of Treatment N	120	115	47	123
Mean (SD)	101.5 (14.16)	106.1 (15.08)	107.0 (13.78)	104.8 (15.64)

Median	98.50	105.00	105.00	102.00
Min, Max	78.0, 177.0	74.0, 174.0	83.0, 141.0	79.0, 173.0
With Diabetes, Baseline N	187	196	45	185
Mean (SD)	146.7 (47.93)	152.1 (48.14)	149.6 (28.48)	148.4 (40.81)
Median	137.00	140.00	149.00	141.00
Min, Max	74.0, 430.0	65.0, 347.0	77.0, 198.0	73.0, 323.0
With Diabetes, End of Treatment N	182	186	38	175
Mean (SD)	149.7 (51.82)	150.1 (45.60)	163.0 (49.40)	151.7 (47.90)
Median	138.00	142.00	158.50	141.00
Min, Max	65.0, 431.0	66.0, 311.0	73.0, 329.0	62.0, 349.0

Source: modified by reviewer from Table 1.11.2-10. of 1.11.2 Safety Information Amendment

In Pool A, in subjects without diabetes there were no meaningful changes between baseline and end of treatment in fasting blood glucose. In subjects with diabetes, there were no meaningful changes between baseline and end of treatment as well, with the possible exception of an arithmetical increase in mean fasting glucose of approximately 18 mg/dL, and a median change of approximately 8.5 mg/dL in the Epanova 3g group.

Table 45 depicts baseline and end of treatment Hemoglobin A1c by treatment group and diabetes status

Table 45: Baseline and Treatment in Hemoglobin A1c by Treatment Group and Diabetes Status — Safety Population from Pool A

Hemoglobin A1c (%)	Olive Oil N=314	Epanova 2g N=315	Epanova 3g N=101	Epanova 4g N=315
Without Diabetes, Baseline N	127	117	56	130
Mean (SD)	5.7 (0.40)	5.7 (0.39)	5.6 (0.38)	5.7 (0.36)
Median	5.70	5.70	5.60	5.70
Min, Max	4.8, 6.4	4.4, 6.4	4.7, 6.4	4.5, 6.4
Without Diabetes End of Treatment N	117	113	46	118
Mean (SD)	5.7 (0.38)	5.7 (0.39)	5.7 (0.40)	5.7 (0.38)
Median	5.70	5.80	5.65	5.70
Min, Max	4.7, 6.8	4.4, 6.9	4.8, 6.8	4.7, 6.8
With Diabetes, Baseline N	187	196	45	185
Mean (SD)	7.1 (1.06)	7.1 (1.01)	7.2 (0.86)	7.1 (0.96)
Median	6.90	6.90	7.10	6.90
Min, Max	5.1, 9.9	5.3, 10.4	5.1, 8.9	5.1, 9.6
With Diabetes, End of Treatment	176	178	38	167

N				
Mean (SD)	7.2 (1.21)	7.2 (1.19)	7.3 (1.09)	7.2 (1.24)
Median	6.90	7.00	7.15	6.90
Min, Max	5.1, 11.1	5.3, 12.1	5.2, 10.8	5.1, 11.9

Source: modified by reviewer from Table 1.11.2-9. of 1.11.2 Safety Information Amendment

In Pool A, There were no meaningful changes between baseline and end of treatment in fasting blood glucose and hemoglobin A1c in subjects without diabetes and in subjects with diabetes.

Reviewer's note: The exploratory analyses presented above were triggered by a numerical difference observed in study 003 in TEAES potentially representing worsening of diabetes between the olive oil group, 1.0% and the Epanova 4 g group, 5.1%. These analyses did not support the existence of a relationship between Epanova 4 g and type 2 diabetes mellitus. It is entirely possible that the numerical difference in TEAEs was due to pure chance. It should be noted however that the studies were small and relatively short, and that these were post-hoc analyses with conceivably very limited statistical power to detect an effect of Epanova at the highest dose on type 2 diabetes, if this hypothetical effect existed.

Pool B: Subjects with Crohn's disease

Table 46: Treatment-Emergent Adverse Event of Special Interest: Hyperglycemia Occurring in >1 Subject by System Organ Class and Preferred Term in Pool B (Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

System Organ Class Preferred Term	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any hyperglycemia	11 (3.0)	14 (3.2)
Investigations	8 (2.2)	8 (1.9)
Weight decreased	6 (1.6)	7 (1.6)
Weight increased	2 (0.5)	1 (0.2)
Metabolism and nutrition disorders	3 (0.8)	5 (1.2)
Dehydration	1 (0.3)	2 (0.5)
Hypercholesterolaemia	0	2 (0.5)
Increased appetite	2 (0.5)	0
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Note: AEs were coded using MedDRA version 14.1. Source: Table 3.14.3.1		

Source: from Sponsor, Table 2.7.4-27, Summary of Clinical Safety.

In Pool B, the proportion of subjects with the listed preferred terms was not different in the two groups.

Reviewer’s note: Differently from subjects with hypertriglyceridemia, in subject with Crohn’s disease Epanova 4g did not seem to be associated with more preferred terms suggestive of diabetes mellitus. As reported earlier, preferred terms suggestive of type 2 diabetes were two-fold more common in the Epanova group vs. the olive oil group in subjects with hypertriglyceridemia; the difference between Pool A and Pool B is likely due to the to the nature (hypertriglyceridemia) of the condition studied in Pool A, as well as to the different mean age (younger subjects in pool B and C) of the subjects.

Pool C: Subjects with Crohn’s disease, Long-Term Exposure

Table 47: Treatment-Emergent Adverse Event of Special Interest: Hyperglycemia by System Organ Class and Preferred Term Safety Population Pool C: Long Term exposure from EPIC-1, EPIC 2, EPIC-3, and EPIC 1E

System Organ Class Preferred Term	Epanova 4g (N=193) n (%)
Any Hyperglycemia	4 (2.1)
INVESTIGATIONS	2 (1.0)
WEIGHT DECREASED	1 (0.5)
WEIGHT INCREASED	1 (0.5)
METABOLISM AND NUTRITION DISORDERS	2 (1.0)
HYPERCHOLESTEROLAEMIA	1 (0.5)
TYPE 2 DIABETES MELLITUS	1 (0.5)

Source: from Sponsor, Table 3.14.4.1 of the Integrated Summary of Safety.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Pool A: Subjects with Hypertriglyceridemia

Table 48: Treatment-Emergent Adverse Events Occurring in >1% in Total Epanova Compared or Placebo (Olive Oil) in Pool A (Studies OM-EPA-003 and OM-EPA 004)

System Organ Class Preferred Term	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99) n (%)	EPANOVA (N = 300) n (%)	Olive Oil (N = 215) n (%)	EPANOVA (N = 431) n (%)	Olive Oil (N = 314) n (%)	EPANOVA (N = 731) n (%)
Any treatment-emergent AE	26 (26.3)	124 (41.3)	60 (27.9)	161 (37.4)	86 (27.4)	285 (39.0)
Gastrointestinal disorders	7 (7.1)	66 (22.0)	19 (8.8)	87 (20.2)	26 (8.3)	153 (20.9)
Diarrhoea	2 (2.0)	25 (8.3)	5 (2.3)	49 (11.4)	7 (2.2)	74 (10.1)
Nausea	1 (1.0)	19 (6.3)	3 (1.4)	19 (4.4)	4 (1.3)	38 (5.2)
Eructation	1 (1.0)	11 (3.7)	0	12 (2.8)	1 (0.3)	23 (3.1)
Abdominal pain	3 (3.0)	6 (2.0)	3 (1.4)	8 (1.9)	6 (1.9)	14 (1.9)
Vomiting	1 (1.0)	6 (2.0)	0	8 (1.9)	1 (0.3)	14 (1.9)
Dyspepsia	0	5 (1.7)	3 (1.4)	5 (1.2)	3 (1.0)	10 (1.4)
Flatulence	0	1 (0.3)	0	9 (2.1)	0	10 (1.4)
Abdominal pain upper	1 (1.0)	6 (2.0)	0	3 (0.7)	1 (0.3)	9 (1.2)
Infections and infestations	11 (11.1)	32 (10.7)	21 (9.8)	31 (7.2)	32 (10.2)	63 (8.6)
Nasopharyngitis	2 (2.0)	11 (3.7)	0	7 (1.6)	2 (0.6)	18 (2.5)
Upper respiratory tract infection	1 (1.0)	2 (0.7)	5 (2.3)	6 (1.4)	6 (1.9)	8 (1.1)
Bronchitis	0	1 (0.3)	5 (2.3)	4 (0.9)	5 (1.6)	5 (0.7)
Musculoskeletal and connective tissue disorders	6 (6.1)	14 (4.7)	11 (5.1)	17 (3.9)	17 (5.4)	31 (4.2)
Arthralgia	1 (1.0)	7 (2.3)	2 (0.9)	2 (0.5)	3 (1.0)	9 (1.2)
Back pain	2 (2.0)	1 (0.3)	3 (1.4)	2 (0.5)	5 (1.6)	3 (0.4)
Nervous system disorders	0	15 (5.0)	3 (1.4)	10 (2.3)	3 (1.0)	25 (3.4)
Dysgeusia	0	4 (1.3)	0	5 (1.2)	0	9 (1.2)
Headache	0	6 (2.0)	0	3 (0.7)	0	9 (1.2)
Metabolism and nutrition disorders	2 (2.0)	5 (1.7)	5 (2.3)	10 (2.3)	7 (2.2)	15 (2.1)
Diabetes mellitus	1 (1.0)	3 (1.0)	3 (1.4)	4 (0.9)	4 (1.3)	7 (1.0)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities
 Note: AEs were coded using MedDRA version 14.1.
 Source: [Table 3.3.1.1](#).

Source: from Sponsor, Table 2.7.4-9, Summary of Clinical Safety.

Both for the olive oil group and the Epanova group, the most commonly reported TEAEs included diarrhea, abdominal pain, nausea and eructation. Other common AEs included nasopharyngitis, arthralgia, and dysgeusia. The incidence of TEAEs was smaller in the olive oil group compared to the pooled Epanova groups (Study 003: 26% vs. 41%; Study 004: 28% vs. 37%; combined studies 27% vs. 39%). The TEAEs occurring at a

threshold of >1% were mapped to the following SOCs: gastro-intestinal disorders, infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, and metabolism and nutrition disorders.

The preferred term dysgeusia was reported by the applicant nine times and it was mapped to the SOC nervous system disorders. In this nine cases this preferred terms was reported exclusively in the Epanova group. Because of this dichotomous distribution, unlikely to have occurred by mere chance, this reviewer decided to further investigate. The table below was created by searching the adverse event listing by putting searching by the word “dysgeusia”, as well as by the word “taste”.

Table 49: Adverse Event terms by “Dysgeusia”, and “Taste” in Study 003

Patient Number	Treatment Group	AE term	System Organ Class/ Preferred Term	Action Taken With Investigational Product	Outcome
007-011	Epanova 4g	FISHY TASTE	Nervous system disorders/ Dysgeusia	Dose Not Changed	Not Recovered/Not Resolved
020-011	Epanova 3g	FISHY TASTE IN MOUTH, INTERMITTENT	Nervous system disorders/ Dysgeusia	Dose Not Changed	Recovered/Resolved
101-015	Epanova 3g	FOUL TASTE	Nervous system disorders/ Dysgeusia	Drug Interrupted	Recovered/Resolved
101-015	Epanova 3g	FOUL TASTE	Nervous system disorders/ Dysgeusia	Drug Withdrawn	Recovered/Resolved
113-008	Epanova 2g	MACKEREL TASTE	Nervous system disorders/ Dysgeusia	Dose Not Changed	Recovered/Resolved
005-005	Epanova 3g	BELCHING WITH FISH TASTE	Gastrointestinal disorders/ Eructation	Dose Not Changed	Recovered/Resolved
112-003	Epanova 4g	BURPING WITH TASTE OF FISH	Gastrointestinal disorders/ Eructation	Dose Not Changed	Recovered/Resolved
112-006	Epanova 2g	BURPING TASTE OF FISHOIL	Gastrointestinal disorders/ Eructation	Dose Not Changed	Recovered/Resolved
112-014	Epanova 4g	BURPING WITH TASTE OF	Gastrointestinal disorders/ Eructation	Dose Not Changed	Recovered/Resolved

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		FISH ONCE			
113-016	Epanova 3g	FISH TASTE IN THE MOUTH AFTER TAKING MEDICATION	General disorders and administration site conditions/ Product taste abnormal	Dose Not Changed	Recovered/Resolved

Source: created by reviewer.

In study 003, the search by the word dysgeusia and the word “taste” elicited 10 AEs in 9 subjects. Five AEs were mapped to the nervous system disorders, four AEs were mapped to gastrointestinal disorders and one to general disorders and administration. All 10 AEs were reported in subjects taking Epanova: two in the Epanova 2g group, five in the Epanova 3g group, and three in the Epanova 4g group.

Table 50: Adverse Event terms by “Dysgeusia”, and “Taste” in Study 004

Patient Number	Treatment Group	Event	Preferred Term/ System Organ Class/	Outcome	Action Taken With Investigational Product
008-005	Epanova 4g	BAD TASTE IN MOUTH 2HRS AFTER TAKING STUDY DRUG	DYSGEUSIA/ NERVOUS SYSTEM DISORDERS	Recovered/Resolved	Dose Not Changed
013-001	Epanova 4g	FISHY TASTE IN MOUTH, INTERMITTENT	DYSGEUSIA/ NERVOUS SYSTEM DISORDERS	Recovered/Resolved	Dose Not Changed
013-007	Epanova 4g	FISHY TASTE IN MOUTH,	DYSGEUSIA/ NERVOUS SYSTEM DISORDERS	Recovered/Resolved	Dose Not Changed
013-026	Epanova 4g	FISHY TASTE IN MOUTH, INTERMITTENT	DYSGEUSIA/ NERVOUS SYSTEM DISORDERS	Recovered/Resolved	Dose Not Changed
016-004	Epanova 4g	METALLIC TASTE IN MOUTH/	DYSGEUSIA/ NERVOUS SYSTEM DISORDERS	Recovered/Resolved	Dose Not Changed
021-007	Epanova 2g	BELCHING FISHY TASTE AFTER TAKING STUDY DRUG	ERUCTATION/ GASTROINTESTINAL DISORDERS	Recovered/Resolved	Dose Not Changed
044-002	Epanova 2g	BELCHING WITH FISH OIL TASTE	ERUCTATION/ GASTROINTESTINAL DISORDERS	Recovered/Resolved	Dose Not Changed
063-007	Epanova 2g	BELCHING "FISHY" TASTE	ERUCTATION/ GASTROINTESTINAL DISORDERS	Recovered/Resolved	Dose Not Changed
013-008	Epanova	INTERMITTENT	ERUCTATION/	Recovered/Resolved	Dose Not

	4g	FISHY TASTE WITH BURPING	GASTROINTESTINAL DISORDERS		Changed
013-020	Epanova 4g	FISHY TASTE WITH BURPING, INTERMITTENT	ERUCTATION/ GASTROINTESTINAL DISORDERS	Recovered/Resolved	Dose Not Changed
024-009	Epanova 4g	BELCHING (FISH TASTE)	ERUCTATION/ GASTROINTESTINAL DISORDERS	Recovered/Resolved	Dose Withdrawn

Source: created by reviewer.

In study 004, the search by the word dysgeusia and the word “taste” elicited 11 AEs in 11 subjects. Five AEs were mapped to the nervous system disorders, and six AEs were mapped to gastrointestinal disorders. All 11 AEs were reported in subjects taking Epanova: three in the Epanova 2g group, and the remaining eight in the Epanova 4g group.

In pool A therefore, the overall incidence of the AE reported above was 2.8% (21/731) in the pooled Epanova group and 0% in the olive oil group. In the three Epanova dose groups the incidence was the following: Epanova 2g 1.6% (5/315); Epanova 3g 4.9% (5/101); Epanova 4g 3.4% (11/315).

Reviewer’s note: The AE terms reported above were exclusively reported in the Epanova group and more often at the Epanova 3g and Epanova 4g compared to the Epanova 2g dose. This reviewer concludes that these AEs were definitely due to the study drug and possibly observed more often at the higher doses.

To further characterize the safety and tolerability profile, reported in Table 51 is the incidence of severe TEAEs in Pool A.

Table 51: Incidence of Severe AEs in Study 003 and Study 004

	Treatment	AE term	System Organ Class
Study 003			
	Epanova 3g	Coronary artery disease with chest pain	Cardiac disorder
	Epanova 2g	Entire body hives	Skin and subcutaneous tissue disorders
	Olive oil	Abdominal pain	Gastrointestinal disorders
	Epanova 4g	Diarrhea	Gastrointestinal disorders
	Epanova 3g	Pulmonary embolism	Respiratory, thoracic and mediastinal disorders
	Olive oil	Worsening of hypertension	Vascular disorders

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	Olive oil	Worsening high triglycerides	Investigations
	Olive oil	Ear infection	Infections and infestations
	Olive oil	Acute sinusitis	Infections and infestations/
	Epanova 3g	Replacement of ICD	Surgical and medical procedures
	Epanova 2g	Urine microalbuminuria	renal and urinary disorders
Study 004			
	Epanova 4g	Coronary artery disease	Cardiac disorders
	Epanova 4g	Abdominal pain upper	Gastrointestinal disorders
	Olive Oil	diarrhea	Gastrointestinal disorders
	Epanova 4g	diarrhea	Gastrointestinal disorders
	Epanova 4g	diarrhea	Gastrointestinal disorders
	Epanova 4g	diarrhea	Gastrointestinal disorders
	Epanova 4g	diarrhea	Gastrointestinal disorders
	Epanova 4g	diarrhea	Gastrointestinal disorders
	Epanova 2g	Diverticular perforation	Gastrointestinal disorders
	Olive Oil	Intestinal obstruction	Gastrointestinal disorders
	Olive Oil	Pneumonia Mycoplasmal	Infections and Infestations
	Olive Oil	hyperglycemia	Metabolism and nutrition disorders
	Epanova 2g	Osteoarthritis	Musculoskeletal and connective tissue disorders
	Epanova 2g	Cystitis interstitial	Renal and urinary disorders
	Epanova 4g	nephrolithiasis	Renal and urinary disorders

Source, created by reviewer.

In Study 003, 5 of the 11 severe AEs took place in the olive oil group, and the remaining in the Epanova group (Epanova 2g: n=2; Epanova 3g: n=3; Epanova 4g: n=1). In Study 004, 14 severe AEs were reported: 4 in the olive oil group and 10 in the Epanova groups. Out of the 25 severe AEs recorded in pool A, the most affected system organ class was the gastrointestinal system with 10 severe AEs, 7 of which took place at the highest Epanova dose 4g. In addition, the cardiac disorder system, the infections and infestations and the renal and urinary disorder system, were all represented with 2 severe AEs each.

Reviewer’s note: Most of the gastrointestinal severe AEs were recorded in the Epanova 4g group; therefore the 4g Epanova dose appears to be associated with worse gastrointestinal tolerability than the Epanova 2g dose.

Pool B: Subjects with Crohn’s disease

Table 52: Summary of Treatment-Emergent Adverse Events in Pool B (Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any treatment-emergent AE	327 (87.9)	369 (85.4)
Serious	33 (8.9)	51 (11.8)
Severe	60 (16.1)	73 (16.9)
Fatal	1 (0.3)	0
Related to study product	77 (20.7)	127 (29.4)
Serious and related to study product	0	0
Leading to study drug discontinuation	155 (41.7)	166 (38.4)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Note: AEs were coded using MedDRA version 14.1. Source: Table 3.1.3.1		

Source: from Sponsor, Table 2.7.4-7, Summary of Clinical Safety.

The incidence of any TEAEs was similar in the placebo and in the Epanova 4g group (87.8% vs. 85.4%). Similarly, TEAEs serious, severe, and leading to study drug discontinuation were not different in the two groups.

Reviewer’s note: In Pool B the incidence of TEAEs was higher than in Pool A, due to the different nature of the condition.

Table 53 lists the TEAEs occurring in $\geq 3\%$. The different threshold used in pool B compared to pool A is due to the higher incidence of TEAEs in this pool.

Table 53: Treatment-Emergent Adverse Events Occurring in $>3\%$ and in Greater Percentage in EPANOVA Compared with Placebo in Pool B (Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

System Organ Class Preferred Term	Placebo (N = 372) n (%)	EPANOVA 4g (N = 432) n (%)
Any treatment emergent adverse event	327 (87.9)	369 (85.4)
Gastrointestinal disorders	272 (73.1)	307 (71.1)
Abdominal pain	83 (22.3)	118 (27.3)
Diarrhoea	48 (12.9)	87 (20.1)
Nausea	23 (6.2)	53 (12.3)
Abdominal distension	17 (4.6)	27 (6.3)
Dyspepsia	18 (4.8)	23 (5.3)
Vomiting	13 (3.5)	22 (5.1)
Constipation	11 (3.0)	21 (4.9)
Frequent bowel movements	12 (3.2)	19 (4.4)
Infections and infestations	135 (36.3)	159 (36.8)
Nasopharyngitis	40 (10.8)	56 (13.0)
Gastroenteritis	15 (4.0)	18 (4.2)
Musculoskeletal and connective tissue disorders	91 (24.5)	105 (24.3)
Arthralgia	43 (11.6)	60 (13.9)
Back pain	19 (5.1)	23 (5.3)
General disorders and administration site conditions	63 (16.9)	78 (18.1)
Fatigue	28 (7.5)	39 (9.0)
Pyrexia	12 (3.2)	16 (3.7)
Asthenia	10 (2.7)	14 (3.2)
Nervous system disorders	50 (13.4)	61 (14.1)
Dysgeusia	3 (0.8)	13 (3.0)
Blood and lymphatic system disorders	11 (3.0)	21 (4.9)
Anaemia	7 (1.9)	14 (3.2)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Note: AEs were coded using MedDRA version 14.1. Source: Table 3.3.3.1		

Source: from Sponsor, Table 2.7.4-12, Summary of Clinical Safety.

Diarrhea, nausea, and vomiting were approximately two-fold higher in the Epanova 4g group than in the Olive Oil group.

Reviewer's note: Albeit these symptoms are expected in Crohn's disease, their preponderance in the Epanova 4g group is suggestive of a drug-related side effect which is consistent with the overall safety and tolerability profile of this drug.

Pool C: Subjects with Crohn’s disease, Long-Term Exposure

Table 54: Summary of Treatment-Emergent Adverse Events in Pool C (Long-Term Exposure from Studies EPIC-1, EPIC-2, EPIC-3, and EPIC-1E)

	EPANOVA 4g (N=193) n (%)
Any treatment-emergent AE	158 (81.9)
Serious	21 (10.9)
Severe	26 (13.5)
Fatal	0
Related to study product	55 (28.5)
Serious and related to study product	0
Leading to study drug discontinuation	12 (6.2)
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities Note: AEs were coded using MedDRA version 14.1. Source: Table 3.1.4.1	

Source: from Sponsor, Table 2.7.4-8, Summary of Clinical Safety.

Reviewer’s comment: The lack of a control group in Pool C makes it hard to establish whether there was an excess of TEAEs in the Epanova 4g group, above the background incidence typical of Crohn’s disease.

7.4.2 Laboratory Findings

Blood and other bodily fluids were sampled at specified time points depending on the parameter. Fasting lipids were measured at every visit, serum chemistry and hematology at baseline and end-of-treatment. Samples were sent to a central laboratory for analysis with the exclusion of urine for pregnancy test. In subjects with hypertriglyceridemia blood samples were drawn at week minus 2 and week 8 in study 003, and at week minus 2 and week 6 in study 004 to determine the following hematology parameters

Hematology

Hematology parameters included white blood cell count and differential, hemoglobin, hematocrit, platelet counts, PT, PTT.

This reviewer conducted for the following parameters, hemoglobin, leukocytes, neutrophils, and platelets a qualitative review of the changes between baseline and post-baseline (so called “shifts”) graded 0-4, according to the NCI-CTC (ref. Table 4.8.1.1, ISS). No subject had grade 3 or 4 neither at baseline nor at the last-observation. Using a lower threshold, grade 2, for hemoglobin there were 2 subjects both in the Epanova group with grade 2, one subject in the Epanova group with grade 2 leukocyte, one subjects in the Epanova group with grade 2 neutrophils, and no subjects for platelets with grade 2.

Biochemistry

Blood samples were drawn for at baseline (Week minus 2) and end of treatment (Week 12 for study 003 and Week 6 for study 004) to determine concentrations of the following biochemistry parameters: sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, calcium, phosphate, total protein, albumin, creatine kinase, AST, ALT, alkaline phosphatase and total bilirubin, and glomerular filtration rate.

This applicant presented the number and percent of subjects with “potentially clinically significant” abnormal chemistry values, defined by changes in CTC grade as defined in the footnote in Table 55 below. The identified changes in the safety population for Pool A are shown.

There were no cases meeting the biochemical definition of Hy’s Law.

Table 55: Potentially Clinically Significant Serum Chemistry Laboratory Values in Pool A (Studies OM-EPA-003 and OM-EPA-004)

Laboratory Parameter	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99)	EPANOVA (N = 300)	Olive Oil (N = 215)	EPANOVA (N = 431)	Olive Oil (N = 314)	EPANOVA (N = 731)
Creatine kinase (U/L)	0	1 (0.3)	0	0	0	1 (0.1)
Glucose (mmol/L)	2 (2.0)	3 (1.0)	9 (4.2)	17 (3.9)	11 (3.5)	20 (2.7)
Phosphate (mmol/L)	0	0	0	1 (0.2)	0	1 (0.1)

CTC = Common Terminology Criteria
 Potentially clinically significant laboratory abnormality was defined as any value where the baseline CTC grade was missing, 0, 1 or 2, and the post-baseline CTC grade was 3, 4, or 5; or if the baseline CTC grade was 3 or 4 and the post-baseline CTC grade was higher than the baseline CTC grade.
 Source: [Table 4.5.1.1](#)

Source: from Sponsor, Table 2.7.4-26, Summary of Clinical Safety.

There were very few parameters with potentially clinically significant abnormal values.

A similar number and proportion of subjects in the olive oil and Epanova groups had potentially abnormal glucose levels (olive oil: 11 (3.5%) vs. 20 (2.7%)). One subject (0.1%) in the Epanova group had abnormal creatine kinase and one subject in the Epanova group had abnormal phosphate.

This reviewer examined also the number and percent of subjects with potentially clinically significant laboratory abnormalities in the safety population for Pool A (ref. Table 4.6.1.2 ISS). Approximately 4.4% (46/1045) of subjects had potentially clinically significant laboratory abnormalities. Group distribution was as follows: olive oil 5% (16/314), pooled Epanova 4.1% (30/731). Within the Epanova groups the following distribution was observed: Epanova 2g: 5% (16/315); Epanova 3g 3/101 (3%); Epanova 4g 3.5% (11/315). Of the 46 potentially clinically significant laboratory abnormalities, 42 were for glucose, one for phosphate, two for creatine kinase and one for neutrophils. The proportion of subjects with abnormal glucose values was not different in the olive oil and Epanova groups.

Reviewer’s note: The proportion of subjects with potentially clinically significant laboratory abnormalities was overall limited and similar in the olive oil and in the Epanova pooled groups. There was no evidence of dose-response increases in the Epanova individual groups and no evidence on greater incidence of abnormal glucose values in the Epanova pooled group.

Table 56: Measures of Central Tendency for Fasting Glucose and Hemoglobin A1c in Study 003

Fasting Glucose (mg/dL)	Olive oil		Epanova 2g		Epanova 3g		Epanova 4g	
	BL	End	BL	End	BL	End	BL	End
Mean (SD)	117.3 (36.50)	121.4 (42.07)	123.6 (42.42)	122.1 (41.01)	126.2 (34.95)	131.0 (43.48)	124.5 (43.29)	127.6 (47.17)
Median	104.0	107.0	110	107.5	114.0	115.0	108.5	109.0
Min, Max	81.0, 297.0	75.0, 310	65.0, 296.0	66.0, 311.0	75.0, 230.0	73.0, 329.0	79.0, 267.0	79.0, 351.0
Hemoglobin A1c (%)	BL	End	BL	End	BL	End	BL	End
Mean (SD)	6.0 (1.01)	6.1 (1.13)	6.1 (0.96)	6.2 (1.10)	6.2 (1.02)	6.4 (1.11)	6.1 (1.02)	6.2 (1.17)
Median	5.7	5.8	5.8	5.9	5.9	6.1	5.7	5.8

BL= baseline
 End= end of treatment

Source: created by reviewer based on Table 12.7 of the Clinical Study Report

Table 57: Measures of Central Tendency for Fasting Glucose and Hemoglobin A1c in Study 004

	Olive oil	Epanova 2g	Epanova 4g
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Fasting Glucose (mg/dL)	BL	End	BL	End	BL	End
Mean (SD)	135.5 (45.39)	133.2 (47.20)	140.2 (45.64)	138.4 (44.76)	133.1 (40.58)	134.1 (43.68)
Median	126	122	129.0	127.0	126.0	123.5
Min, Max	64 394	65 431	55 388	68 360	70 311	62 349
Hemoglobin A1c (%)						
Mean (SD)	6.72 (1.07)	6.75 (1.17)	6.80 (1.04)	6.84 (1.15)	6.68 (1.02)	6.74 (1.24)
Median	6.40	6.50	6.60	6.60	6.50	6.40
Min, Max	5.0 9.9	5.1 11.1	5.0 10.0	5.1 10.9	5.0 9.6	5.0 11.9
BL= baseline End= end of treatment						

Source: created by reviewer based on table 14.3.4.1 of Study 004 CSR.

Table 58: Grades 1-4 for Hyperglycemia

	Grade 1	Grade 2	Grade 3	Grade 4
Hyperglycemia	ULN - <=8.9 (mmol/L)	>8.9 - <=13.9 (mmol/L)	>13.9 - <=27.8 (mmol/L)	>27.8 (mmol/L)

Source: Table of NCI CTC Grades for Laboratory Values (SI Units), version 4.0 June 2010.

Table 59 indicates the criteria used by the Sponsor to define the shift from normal to abnormal lower or higher values for fasting glucose.

Table 59: Shift from Normal to Abnormal Lower or Higher Results for Fasting Glucose by Maximum NCI-CTC Grade Safety Population for Study 003

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 EPANOVA (omega-3-carboxylic acids)

Post-baseline (Last Observation)											
OM-EPA-003 Olive Oil (N=99) n (%)											
		Abnormal Low			Normal			Abnormal High			
Laboratory Parameter	Category	Baseline	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Glucose (mmol/L)											
Low	Grade 4		0	0	0	0	0	0	0	0	0
	Grade 3		0	0	0	0	0	0	0	0	0
	Grade 2		0	0	0	0	0	0	0	0	0
	Grade 1		0	0	0	0	0	0	0	0	0
Normal	Grade 0		0	0	0	0	50 (54.9)	11 (12.1)	1 (1.1)	0	0
	Grade 1		0	0	0	0	5 (5.5)	9 (9.9)	5 (5.5)	0	0
	Grade 2		0	0	0	0	0	3 (3.3)	4 (4.4)	2 (2.2)	0
	Grade 3		0	0	0	0	0	1 (1.1)	0	0	0
High	Grade 4		0	0	0	0	0	0	0	0	0
	Grade 3		0	0	0	0	0	0	0	0	0
	Grade 2		0	0	0	0	0	0	0	0	0
	Grade 1		0	0	0	0	0	0	0	0	0

OM-EPA-003 Epanova (N=300) n (%)											
		Abnormal Low			Normal			Abnormal High			
Laboratory Parameter	Category	Baseline	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Glucose (mmol/L)											
Low	Grade 4		0	0	0	0	0	0	0	0	0
	Grade 3		0	0	0	0	0	0	0	0	0
	Grade 2		0	0	0	0	0	0	0	0	0
	Grade 1		0	0	0	0	0	0	0	0	0
Normal	Grade 0		0	0	0	0	129 (48.0)	19 (7.1)	6 (2.2)	0	0
	Grade 1		0	0	0	0	27 (10.0)	35 (13.0)	19 (7.1)	0	0
	Grade 2		0	0	0	0	3 (1.1)	5 (1.9)	18 (6.7)	3 (1.1)	0
	Grade 3		0	0	0	0	0	1 (0.4)	1 (0.4)	3 (1.1)	0
High	Grade 4		0	0	0	0	0	0	0	0	0
	Grade 3		0	0	0	0	0	0	0	0	0
	Grade 2		0	0	0	0	0	0	0	0	0
	Grade 1		0	0	0	0	0	0	0	0	0

		Post-baseline (Last Observation)									
		OM-EPA-004 Olive Oil (N=215) n (%)									
		Abnormal Low			Normal			Abnormal High			
Laboratory Parameter	Category	Baseline	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Glucose (mmol/L)											
Low	Grade 4	0	0	0	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0	0	0	0	0
Normal	Grade 0	0	0	0	0	0	83 (39.3)	9 (4.3)	1 (0.5)	1 (0.5)	0
	Grade 1	0	0	0	0	0	8 (3.8)	56 (26.5)	11 (5.2)	1 (0.5)	0
	Grade 2	0	0	0	0	0	0	10 (4.7)	23 (10.9)	4 (1.9)	0
	Grade 3	0	0	0	0	0	0	2 (0.9)	1 (0.5)	1 (0.5)	0
High	Grade 4	0	0	0	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0	0	0	0	0

		OM-EPA-004 Epanova (N=431) n (%)									
		Abnormal Low			Normal			Abnormal High			
Laboratory Parameter	Category	Baseline	Grade 4	Grade 3	Grade 2	Grade 1	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Glucose (mmol/L)											
Low	Grade 4	0	0	0	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0	0	0	0	0
Normal	Grade 0	0	0	0	0	0	130 (31.4)	26 (6.3)	2 (0.5)	0	0
	Grade 1	0	0	0	0	0	34 (8.2)	113 (27.3)	27 (6.5)	1 (0.2)	0
	Grade 2	0	0	0	0	0	2 (0.5)	16 (3.9)	45 (10.9)	10 (2.4)	0
	Grade 3	0	0	0	0	0	1 (0.2)	1 (0.2)	5 (1.2)	1 (0.2)	0
High	Grade 4	0	0	0	0	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0	0	0	0	0
	Grade 2	0	0	0	0	0	0	0	0	0	0
	Grade 1	0	0	0	0	0	0	0	0	0	0

Source: Table 4.7.1.2, Integrated Summary of Safety

In Study 003, in the olive oil group, two subjects with Grade 2 abnormal high at baseline had Grade 3 abnormal high at post-baseline; in the Epanova group, three subjects with Grade 3 abnormal high at baseline had Grade 3 abnormal high at post-baseline.

In Study 004, in the olive oil group four subjects with Grade 2 abnormal high at baseline Developed Grade 3 abnormal high at post-baseline; in the Epanova group, ten subjects with Grade 2 abnormal high at baseline developed Grade 3 abnormal high at post-baseline.

Reviewer's note: The numbers are too small to attempt any inference on whether treatment with Epanova changes the proportion of subjects with high fasting glucose.

Lipids

Blood was drawn for fasting lipid panels (serum TG, total cholesterol, direct LDL-C, HDL-C, calculated non-HDL-C, VLDL-C and TC: HDL ratio) at every visit and for fasting special lipid panel (serum apo A-I, apo-B, apo C-III, Lp-PLA2 and lipoprotein particles) three times: before randomization, at the randomization visit and at the last study visit. For greater details on this topic please refer to Dr. Iffat Chowdhury's clinical efficacy review.

Urinalysis

Urine samples were collected at screening and at the end of the trial. Urine chemical analysis included glucose, bilirubin, ketone, specific gravity, pH, blood, protein, urobilinogen, nitrite and leukocyte esterase. There were no changes from baseline in urinalysis. In terms of “missing” values the follow-up urinalysis was performed in 89% (939/1044) of the original sample (source: Table 4.3.1.1, ISS).

Liver enzymes

Pool A: Subjects with Hypertriglyceridemia

Table 60: Measures of Central Tendency in Liver Enzymes in Subjects with Hypertriglyceridemia

Laboratory Parameter (unit)	Visit Statistics	OM-EPA-003		OM-EPA-004		Total	
		Olive Oil (N=99)	Epanova (N=300)	Olive Oil (N=215)	Epanova (N=431)	Olive Oil (N=314)	Epanova (N=731)
Alanine Aminotransferase (U/L)							
Baseline							
n		99	300	214	431	313	731
Mean (SD)		35.6(15.45)	38.1(19.06)	31.5(13.75)	33.1(15.01)	32.8(14.41)	35.2(16.95)
Median		34.0	34.0	27.0	30.0	29.0	31.0
Min, Max		11.0,86.0	6.0,117.0	11.0,83.0	10.0,100.0	11.0,86.0	6.0,117.0
Final Observation							
n		90	270	202	395	292	665
Mean (SD)		40.4(27.69)	41.4(22.39)	29.2(12.20)	35.9(16.96)	32.7(19.08)	38.1(19.52)
Median		33.5	36.5	27.0	32.0	27.0	34.0
Min, Max		15.0,193.0	10.0,167.0	12.0,75.0	6.0,120.0	12.0,193.0	6.0,167.0
Change from Baseline							
n		90	270	202	395	292	665
Mean (SD)		4.6(24.40)	3.9(15.24)	-2.1(7.62)	3.0(11.61)	0.0(15.22)	3.3(13.20)
Median		-1.0	2.0	-1.5	1.0	-1.0	2.0
Min, Max		-54.0,152.0	-42.0,88.0	-34.0,24.0	-37.0,86.0	-54.0,152.0	-42.0,88.0
Aspartate Aminotransferase (U/L)							
Baseline							
n		99	300	215	431	314	731
Mean (SD)		30.1(10.81)	31.5(13.95)	27.1(10.01)	27.8(10.44)	28.1(10.35)	29.3(12.13)
Median		27.0	28.0	24.0	25.0	25.0	26.0
Min, Max		16.0,77.0	13.0,100.0	13.0,72.0	11.0,85.0	13.0,77.0	11.0,100.0
Final Observation							
n		90	270	203	395	293	665
Mean (SD)		32.8(19.08)	31.7(14.26)	25.8(8.06)	28.4(10.95)	28.0(12.91)	29.7(12.50)
Median		29.0	28.0	24.0	26.0	25.0	27.0
Min, Max		16.0,149.0	13.0,138.0	14.0,59.0	12.0,82.0	14.0,149.0	12.0,138.0
Change from Baseline							
n		90	270	203	395	293	665
Mean (SD)		2.5(17.21)	0.7(10.56)	-0.9(6.25)	0.5(8.23)	0.2(10.94)	0.6(9.24)
Median		0.0	0.0	-1.0	1.0	0.0	1.0
Min, Max		-34.0,115.0	-59.0,48.0	-35.0,18.0	-44.0,38.0	-35.0,115.0	-59.0,48.0

Source: from Table 4.1.1.1, Integrated Summary of Safety.

The changes from baseline in alanine aminotransferase and aspartate aminotransferase were small. Approximately 92% of subjects had repeated values.

This reviewer conducted also analyses of laboratory shifts for alanine aminotransferase and aspartate aminotransferase.

Table 61: Grades 1-4 for ALT and AST

	Grade 1	Grade 2	Grade 3	Grade 4
ALT (SGPT)	>ULN - <=3.0 x ULN	>3.0 - <=5.0 x ULN	>5.0 - <=20.0 x ULN	>20.0 x ULN
AST (SGOT)	>ULN - <=3.0 x ULN	>3.0 - <=5.0 x ULN	>5.0 - <=20.0 x ULN	>20.0 x ULN

Source: Table of NCI CTC Grades For Laboratory Values (SI Units), version 4.0 June 2010.

At baseline, no subject had any grade greater than Grade 0 and Grade 1 for these liver enzymes. Post-baseline, Grade 2 for ALT was reported in the following groups: olive oil (N=2), Epanova 3g (N=1), Epanova 4g (N=1). Post-baseline, Grade 2 for AST was reported in the following groups: olive oil (N=2), Epanova 2g (N=1), and Epanova 3g (N=1). There were no Grade 3 or Grade post-treatment (ref. Table 4.7.2.1, ISS).

Reviewer's note: Based on both measures of central tendency analyses and shift analyses, no evidence of a safety signal for the above parameters in this small safety dataset was detected. The changes observed were small and likely of no clinical significance. The proportion of missing values, 8% was acceptable. The number of subjects with elevations of alanine aminotransferase and aspartate amino transferase was overall limited and similar between the two groups.

Pool B: Subjects with Crohn's disease

Table 62: Liver Enzymes in Subjects with Crohn's Disease

Laboratory Parameter (unit)	Visit Statistics	Placebo (N=372)	Epanova 4g (N=432)
Alanine Aminotransferase (U/L)	Baseline		
	n	369	432
	Mean (SD)	21.8(16.38)	21.4(13.71)
	Median	17.7	18.4
	Min, Max	0.8, 205.5	3.0, 193.3
	Final Observation		
	n	311	344
	Mean (SD)	20.6(14.33)	21.7(13.57)
	Median	16.5	18.3
	Min, Max	-2.8, 149.5	-1.0, 121.5
	Change from Baseline		
	n	311	344
Mean (SD)	-1.8(16.74)	-0.3(13.92)	
Median	-0.7	0.0	
Min, Max	-171.5, 112.0	-126.0, 75.3	

Laboratory Parameter (unit)	Visit Statistics	Placebo (N=372)	Epanova 4g (N=432)
Aspartate Aminotransferase (U/L)	Baseline		
	n	370	432
	Mean (SD)	19.3 (6.58)	19.2 (6.82)
	Median	18.5	18.5
	Min, Max	3.7, 81.4	5.1, 62.3
	Final Observation		
	n	311	344
	Mean (SD)	20.6 (7.56)	20.4 (7.30)
	Median	19.5	19.1
	Min, Max	6.4, 56.4	5.1, 72.2
	Change from Baseline		
	n	311	344
Mean (SD)	1.3 (7.38)	1.3 (7.12)	
Median	0.6	1.2	
Min, Max	-57.9, 39.5	-43.4, 51.3	

Source: Table 4.1.3.1, Integrated Summary of Safety.

The changes from baseline in alanine aminotransferase and aspartate aminotransferase were small. Approximately 81% of subjects had repeated values.

Reviewer's note: The changes observed were small and likely of no clinical significance. The proportion of missing values, 19% was high. This is likely due to the fact that in Pool B the studies were longer and the patient population subjects with Crohn's disease sicker.

This reviewer did not perform a corresponding analysis for pool C.

7.4.3 Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse were assessed at the screening visit and at the end of the trials. Measurements were performed with the subject sitting after having rested in a chair for at least 3 minutes. The first measurement was ignored and the average of the last two measurements was recorded. Any clinically significant worsening of the result from baseline was to be reported as an AE. Potentially clinically significant (PCS) vital signs were defined as follows: systolic blood pressure <100 or \geq 150 mmHG; diastolic blood pressure \geq 90 mmHG; heart rate <60 or >120 beats/min).

Reviewer's note: The Sponsor did not list a definition for abnormally low diastolic blood pressure. This is however of relatively little importance, as the study drug is not likely to be associated with hypotension given the experience with the drug and its mechanism of action.

Pool A: Subjects with Hypertriglyceridemia

Table 63: Mean and Median Changes from Baseline in Vital Signs and Anthropometric Parameters in Pool A (Studies OM-EPA 003 and OM-EPA 004)

Parameter Change from Baseline	OM-EPA-003		OM-EPA-004		Total	
	Olive Oil (N = 99)	EPANOVA (N = 300)	Olive Oil (N = 215)	EPANOVA (N = 431)	Olive Oil (N = 314)	EPANOVA (N = 731)
Diastolic Blood Pressure (mmHg)						
Mean (SD)	1.1 (8.09)	0.2 (7.42)	-1.6 (7.82)	-0.2 (7.74)	-0.8 (7.99)	-0.1 (7.61)
Median	2.0	0.0	-1.0	0.0	0.0	0.0
Systolic Blood Pressure (mmHg)						
Mean (SD)	1.9 (12.26)	0.4 (11.84)	-0.9 (12.20)	-0.2 (12.10)	0.0 (12.26)	0.0 (11.99)
Median	1.0	0.0	-1.0	0.0	0.0	0.0
Heart Rate (beats/min)						
Mean (SD)	1.3 (7.17)	-0.6 (7.91)	0.5 (7.99)	-0.6 (8.13)	0.7 (7.75)	-0.6 (8.04)
Median	1.0	0.0	1.0	-0.5	1.0	0.0
Weight (kg)						
Mean (SD)	-0.3 (2.16)	0.1 (2.77)	-0.2 (1.76)	0.0 (1.99)	-0.3 (1.89)	0.0 (2.32)
Median	0.0	0.0	0.0	0.1	0.0	0.1

SD = standard deviation
 Source: [Table 7.1.1.1](#)

Source: from Sponsor, Table 2.7.4-29, Summary of Clinical Safety.

Changes from baseline in vital signs were very small and of no clinical significance.

This reviewer did not perform a corresponding analysis for pool B and pool C.

7.4.4 Electrocardiograms (ECGs)

A 12-lead ECG was performed at screening and at the end of the trial (12 or 6 weeks) and each ECG was originally read by the investigator at each clinical site. The ECGs were then analyzed by a central laboratory. The Sponsor produced a Cardiac ECG Safety Report which included central tendency and outlier analyses, as well as a morphological analysis. For studies 003 and 004, the Sponsor monitored several relevant ECG parameters (atrial rate, PR intervals, QRS interval, QT interval, ventricular rate); in addition, an investigator's interpretation of ECGs findings was provided for study 004. At baseline, more than 99% of subjects had either normal (2/3) or non-clinically significant abnormal (1/3) ECGs.

The DMEP consulted the QT Interdisciplinary Review Team (QT-IRT), Division of Cardiovascular and Renal Products, to further evaluate the issue of potential proarrhythmic liability:

Protocol OM-EPA-003; EVOLVE is a prospective, double-blind, randomized, parallel 4-arm study assessing 332 subjects under 12 weeks of treatment. Twelve-lead electrocardiograms (ECG) are collected at baseline (Visit 3-week -1) and at steady-state (Visit 8/ET; week 12 on treatment or early termination). The Visit 8 ECG was used to compare to the baseline in each treatment group: placebo, omefas 2, 3 and 4 g/day. ECGs were originally read by the Investigator at each clinical site. Paper ECGs were retrospectively sent to a central laboratory for a blinded high-resolution reading by a central cardiologist blinded to the study treatment. Mean changes from baseline for QTcF, PR and QRS duration placebo-corrected were not clinically meaningful for any of the dose groups (2, 3 and 4 g/d). No subject had a QTcF > 500 ms or a post-baseline increase > 60 ms. No subject had an increase incidence in morphological ECG changes compared to placebo.

The mean change from baseline for heart rate placebo-corrected was not clinically meaningful.

Source: memo dated December 13, 2013 from CDER DCRP QT Interdisciplinary Review Team.

The conclusion of the QT-IRT was that: “ECG data from Protocol OM-EPA-003 do not show proarrhythmic liability for Epanova”

7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies other than those addressed in this review were conducted in the Epanova program.

7.4.6 Immunogenicity

Not applicable

7.5 Other Safety Explorations

7.5.1 Dose- and Time-Dependency for Adverse Events

Table 64 summarizes relevant TEAEs by dose level for Pool A.

Table 64: Relevant TEAEs by Dose Level in Subjects with Hypertriglyceridemia

	Olive Oil N=314	Epanova 2g/d N=315	Epanova 3g/d N=101	Epanova 4g/d N=315	Epanova All doses N=730
Any serious TEAEs	5 (1.6%)	4 (1.3%)	4 (4.0%)	1 (0.3%)	9 (1.2%)
Any TEAEs leading to study drug d/c	2 (0.6%)	7 (2.2%)	7 (6.9%)	12 (3.8%)	26 (3.6%)
Any hemorrhage	3 (1.0%)	2 (0.6%)	4 (4.0%)	4 (1.3%)	10 (1.4%)
"Hemorrhage" = adverse events identified solely by preferred terms in the Hemorrhage SMQ					

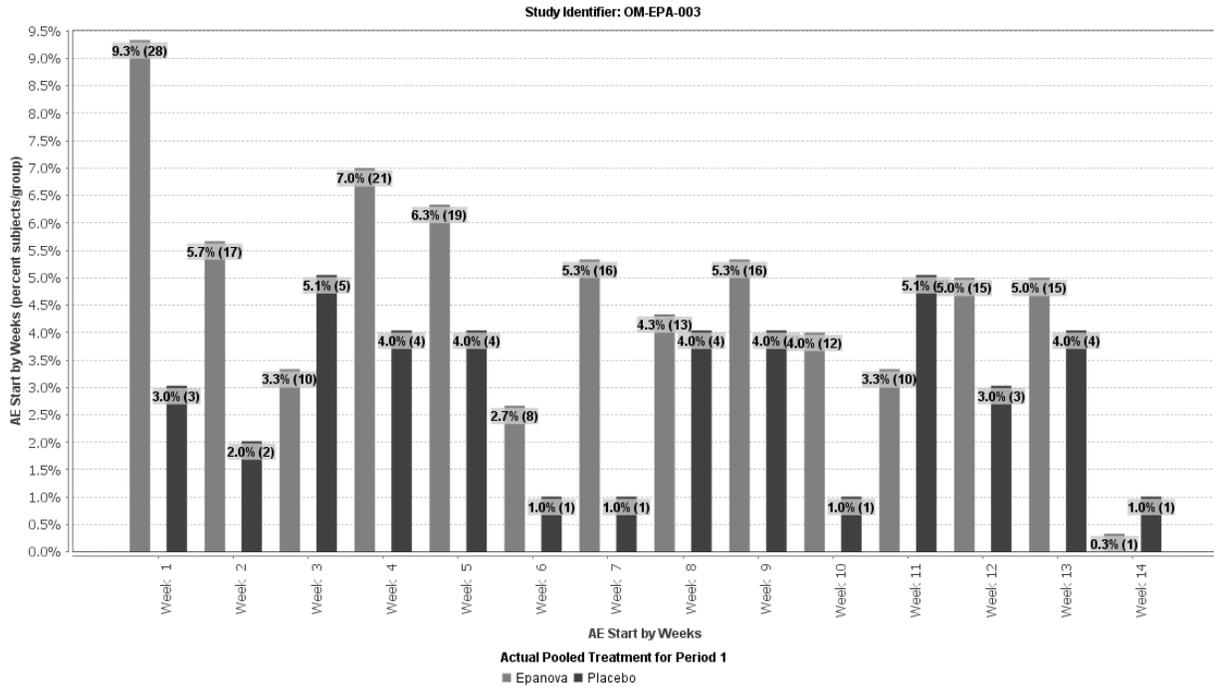
Source: created by reviewer based on the Integrated Summary of Safety.

In pool A, the overall incidence of serious TEAEs was 1.3% (14/1044), of TEAEs leading to study drug d/c 2.7% (28/1044), and of any adverse events potentially due to hemorrhage 1.2% (13/1044). The incidence of any TEAEs leading to study drug d/c in the Epanova 2g group and Epanova 4g group was 2.2% and 3.8%, respectively compared to the olive oil group, 0.6%.

Reviewer's note: The overall incidence of the above TEAEs was limited. This could be a consequence of the relatively healthy study population as well as of the limited duration of the studies in pool A. There were no meaningful differences in the Epanova 2g and Epanova 4g vs. the olive oil group. The findings observed in the Epanova 3g are of difficult interpretation due to relatively small sample size.

Figure 4 characterizes on a weekly basis the temporal pattern of TEAEs in study 003 and study 003.

Figure 4: Percent of Subjects with TEAEs by Onset (Study Week) in Study 003

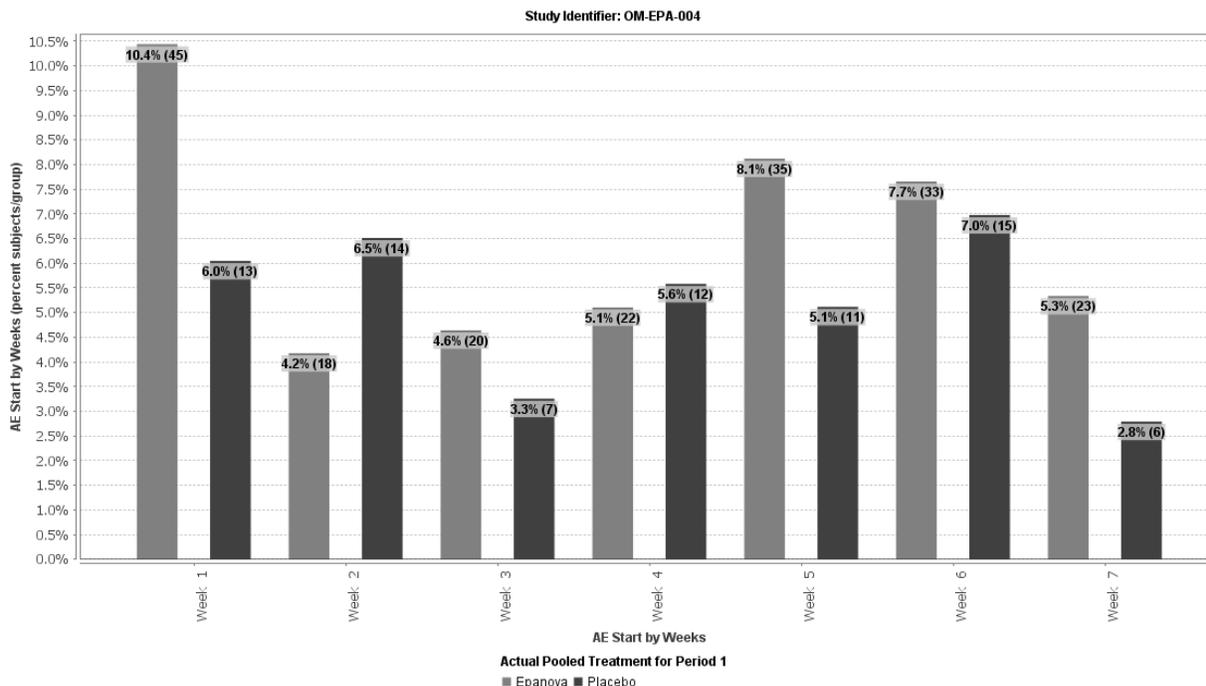


Source: created by reviewer using J review.

In the olive oil the incidence of TEAEs ranged between 1% and 5% per week with no clear temporal pattern. Differently, the following temporal pattern was evident in the Epanova group: the incidence of TEAEs was the highest (9%) on the first week and then it declined up to 5% by Week 7 and remained constant up to Week 13.

Figure 5 characterizes the temporal pattern on a weekly basis of TEAEs in study 004.

Figure 5: Percent of Subjects with TEAEs by Onset (Study Week) in Study 004



Source: created by reviewer using J review.

In study 004, in the olive oil the incidence of TEAEs ranged between 3% and 7% per week with no clear temporal pattern. In the Epanova group the weekly incidence of TEAEs decreased from approximately 10% at Week 1 to 3% by Week 3. In the olive oil group, AE fluctuated over time, with no clear temporal pattern.

Reviewer's note: The temporal pattern of AEs in the Epanova group, particularly evident in study 003 because of the longer duration of this study, supports the hypothesis of a progressive adaptation and better tolerability with time of the subjects to the study drug.

7.5.3 Drug-Demographic Interactions

For the Hypertriglyceridemic, Placebo-Controlled Integrated Dataset, the applicant conducted analyses of TEAEs by gender, age and race.

Table 65 depicts TEAEs by gender, age and race in subjects with hypertriglyceridemia

Table 65: TEAEs by Gender, Age and Race in Subjects with Hypertriglyceridemia

	Olive Oil (N=314) n (%)		Epanova (N=731) n (%)	
	Male	Female	Male	Female
Gender				
Any TEAEs	51 (25.6)	35 (30.4)	189 (38.6)	99 (41.1)
AEs Leading to study drug discontinuation	0	2 (1.7)	17 (3.5)	9 (3.7)
Age	<65	≥65	<65	≥65
Any TEAEs	55 (25.9)	31 (30.4)	217 (39.4)	71 (39.4)
Leading to study drug discontinuation	1 (0.5)	1 (1.0)	23 (4.2)	3 (1.7)
Race	Caucasian	Non-Caucasian¹	Caucasian	Non-Caucasian
Any TEAEs	80 (27.4)	6 (27.2)	265 (38.6)	23 (52.2)
Leading to study drug discontinuation	2 (0.7)	0	24 (3.5)	2 (4.5)

¹Non-Caucasians included Black, Asian and Others

Source: created by reviewer based on Tables 3.1.1.2; 3.1.1.3; and 3.1.1.4 of the Integrated Summary of Safety.

Gender: In pool A, there were 689 males and 356 females. The incidence of any TEAEs was not different for males and females both in the Olive Oil group (25.6% vs. 30.4%) and in the Epanova group (38.6% vs. 41.1%).

Age: In pool A, there were 763 subjects <65 year old and 282 ≥65 old. The incidence of any TEAEs was not different for subjects < 65 vs. subjects ≥65 and both in the Olive Oil group (25.9% vs. 30.4%) and in the Epanova group (39.4% vs. 39.4%).

Race: In pool A, there were 979 Caucasians and 66 non-Caucasians subjects. The incidence of any TEAEs appeared not different for Caucasian subjects vs. non-Caucasian in the Olive Oil group (27.4% vs. 27.2%). In the Epanova group the incidence of any TEAEs appeared numerically higher in non-Caucasian subjects (52.2% vs. 38.6%). The incidence of AEs leading to study drug discontinuation and the overall AE profile was also not different among different races.

Reviewer's note: The number of male and female subjects and of subjects younger and older than 65 year old is adequate to support the observations made above. The small number of non-Caucasian subjects makes any conclusion on the incidence of TEAEs in these races compared to Caucasian subjects quite speculative.

The applicant conducted analyses of TEAEs by diabetes status.

Table 66 depicts TEAEs by diabetes status in subjects with hypertriglyceridemia.

Table 66: Number and Percent of TEAEs by Diabetes Status in the Olive Oil Group in the Epanova Group in Study 003

	Olive Oil		Epanova	
	Non diabetes N=68	Type 2 Diabetes N=31	Non diabetes N=180	Type 2 Diabetes N=120
Subjects experiencing TEAEs	17 (25.0%)	9 (29.0%)	74 (41.1%)	53 (44.2%)

Source: created by reviewer based on Table 1.2.1.1 of the Integrated Summary of Safety.

In the olive oil group, the incidence of TEAEs was 25% vs. 29% in subjects without diabetes vs. subjects with diabetes. In the Epanova group, the incidence of TEAEs was 41% vs. 44% in subjects without diabetes vs. subjects with diabetes.

Reviewer's note: The percent of subjects experiencing TEAEs was not different between subjects with diabetes vs. subjects without diabetes. This was true both for the Epanova as well as the olive oil group.

Drug-Drug Interactions

Concomitant Statin Use

The applicant conducted analyses of TEAEs by statin use.

Table 67: Number and Percent of TEAEs by Statin User Status in the Olive Oil Group and in the Epanova Group in Study 003

	Olive Oil		Epanova	
	Non user N=65	Statin or CAI User N=34	Non user N=196	Statin or CAI User N=104
Subjects experiencing TEAEs	14 (21.5%)	12 (35.2%)	76 (38.8%)	51 (49.0%)

CAI= Cholesterol Absorption Inhibitors

Source: created by reviewer based on Table 1.2.1.1 of the Integrated Summary of Safety.

In the olive oil group, the incidence of TEAEs was 21% vs. 35% in non-statin users vs. statin users. In the Epanova group, the incidence of TEAEs was 39% vs. 49% in non-statin users vs. statin users.

Reviewer's note: TEAEs were more common in statin users vs. non-statin users, both in the olive oil and in the Epanova group.

The applicant conducted studies of drug interaction with the following concomitant medications: warfarin, simvastatin and aspirin, anticoagulants or other drugs affecting coagulation.

Warfarin:

The applicant conducted an open-label drug-interaction study, OM-EPA-006, entitled: An Open-Label 2-Cohort Study to Evaluate the Effect of Multiple Doses of Epanova® on the Single Dose Pharmacokinetics and Pharmacodynamics of Warfarin and to Compare the Systemic Exposure of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Following Multiple-Dose Administration of Epanova® Compared to Lovaza® in Healthy Normal Subjects)

This study was conducted in 52 healthy male or female subjects, age 18-55 years.

The primary objective of study 006 was to evaluate the effects of multiple doses of Epanova on the pharmacokinetics and pharmacodynamics of a single dose (25mg) of warfarin. The secondary objective was to compare the systemic exposure of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) following multiple-dose administration of Epanova compared to multiple-dose administration of Lovaza (omega-3 acid ethyl esters).

There were two cohorts: Cohort 1: Treatment A: Single dose of warfarin w/o Epanova. Treatment B: Single dose of warfarin with 4g QD Epanova. Cohort 2: Treatment C: 4g QD of Lovaza following low fat breakfast. Twenty-six subjects were enrolled in Epanova cohort and 26 subjects were enrolled in the Lovaza cohort. The duration of the study was approximately 29.5 days for subjects in Cohort 1 and approximately 22.5 days for subjects in Cohort 2.

Reported below are the conclusions from the review of Dr. Suryanarayana Sista from the review of Office of Clinical Pharmacology:

“Reviewer Comments:

Epanova administered at a dose of 4 grams/day at steady-state did not significantly affect the single dose AUC or C_{max} of R- and S- warfarin or the anti-coagulation pharmacodynamics (PT INR) of 25 mg warfarin. This study evaluated the drug-drug interaction potential of a steady-state administration of Epanova on a single-dose administration of warfarin. The interaction potential of steady-state administration of Epanova on a steady-state administration of warfarin is unknown. While no dose adjustment for warfarin is required when co-administered with Epanova based on lack of single-dose pharmacokinetic or pharmacodynamic interaction, frequent monitoring of INR in patients on warfarin and/or coumarin derivatives, as well as following of instructions in the warfarin product monograph for appropriate monitoring and dose adjustment is recommended at the time of initiation or ending of Epanova treatment.”

This reviewer concurs with the above recommendations including the of frequent monitoring of INR time in the categories of patients listed in the above statement.

Simvastatin and Aspirin

The applicant conducted an open-label, randomized, 2-way cross-over, 14-day duration, drug-interaction study OM-EPA-007 entitled: "An Open-Label, Randomized, 2-Way Crossover Study to Evaluate the Effect of Multiple Doses of Epanova® on the Multiple-Dose Pharmacokinetics of Simvastatin in Healthy Normal Subjects". This study was conducted in 52 healthy adult male or female subjects. The primary objective of this study was to determine the effect of multiple doses of Epanova on the PK of multiple 40-mg doses of simvastatin and 81 mg of aspirin.

Reported below are the conclusions from the review of Dr. Suryanarayana Sista from the review of Office of Clinical Pharmacology:

“Reviewer Comments:

Concomitant administration of EPA with Simvastatin and aspirin reduced simvastatin total exposure by approximately 13%. Information from the product label for simvastatin (Zocor) for similar DDI based exposure reduction indicates that fenofibrate and propranol decrease simvastatin exposure by about 10% and 20%, respectively. No dosing adjustment was recommended when coadministering simvastatin with fenofibrate or propranol. Similarly, no dosing adjustment is recommended when administering simvastatin with Epanova.”

This reviewer concurs with the above recommendation.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Attached below is an *excerpta* from the review of Dr. Parvaneh Espandiari:

“Two carcinogenicity studies were conducted in rats (2-year) and in Tg.rasH2 mice (26-week) oral (gavage) with omefas. In the Tg.rasH2 mice study, no drug-related tumors up to 2000 mg/kg/day omefas were observed (5 fold safety margin to the MHRD of 4 g/day based on a body surface area comparison).

In the rat study, benign sex cord stromal tumors of the ovaries were reported in 2000mg/kg/day omefas treated females (5 fold to the MHRD of 4g/day based on a body surface area comparison). This finding was statistically significant for both trend ($P=0.0005$) and pairwise comparison ($P=0.0054$). The benign ovarian sex cord tumor at 2000mg/kg/day exceeded concurrent control and historical controls despite deviations from the protocol regarding the early discontinuation of dosing and termination for all treated animals (females were dosed for at least 65 weeks). Mortality for this study was statistically significant and cause of death was non-neoplastic based on microscopic dose-response gavage/reflux-related findings in the respiratory tract.”.

For further details please refer to the pharmacology/toxicology report by Dr. Parvaneh Espandiari.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies of Epanova in pregnant women.

No reports of pregnancy occurred during the studies conducted in subjects with hypertriglyceridemia, OM-003, and OM-004. In the Crohn's disease program eight pregnancies were reported as SAEs, 5 out of 372 subjects in the placebo group, and 3 out of 432 subjects in the Epanova 4g group. Subject 215-28, a 22 year old Caucasian female, had an outcome of miscarriage, which was reported as uterine cramps and abortion spontaneous. Study drug was discontinued due to pregnancy in one subject (placebo group) in EPIC-1, four subjects in EPIC-2 (one Epanova, three placebo) and one subject in EPIC-3 (Epanova). No further details are available on these pregnancies, thus the only known case of miscarriage on Epanova was in Study EPIC-2 in a subject who was in the Epanova 4g group.

In addition, as reported by the Sponsor long-chain polyunsaturated fatty acid (LC-PUFA), including DHA, are essential for the normal development of cell membranes in the CNS which are rich in phospholipids. C-PUFA are taken up actively by the brain during pregnancy and childhood. For this reason, a dietary intake of 200-300 mg/day is recommended during pregnancy. The fetus depends on LC-PUFA, which is mostly received via the placenta. The Sponsor included in support of its application several published studies that are summarized below by this reviewer.

In a double-blind, placebo controlled, 1:1 allocation ratio study conducted in Mexico, 400 mg of DHA or placebo daily were administered to 1094 pregnant women, from 18 to 22 weeks' gestation through parturition [Imhoff-Kunsch et al., 2011]. The number of infants born with congenital anomalies such as spina bifida and heart malformations was similar in the control group (N=15) vs. the DHA group (N=16). In a follow-up study from the same group of women, the following adverse birth outcomes were reported: five stillbirths (3 control, 2 DHA) and 12 infant deaths (8 control, 4 DHA) [Ramikrishnan et al., 2010].

The safety of EPA (in combination with DHA) has been studied in a small randomized, double-blind, placebo controlled study of 63 pregnant (week 12 to week 37 of pregnancy) women with previous history of intrauterine growth retardation who received capsules containing a EPA/DHA mixture (total daily dose of EPA ~3 grams; n=32) or placebo (coconut oil; n=31) [Bulstra-Ramakers et al. 1994]. There were 2 fetal deaths in the EPA group vs. 4 fetal deaths in the control group. Neonatal birth weight and other pregnancy outcomes were not different between groups.

Use in Lactation

As noted by the Sponsor, omega-3-free fatty acids are detectable in human milk. An adequate amount of omega-3-free fatty acids may be important for the development of retina and brain [Jensen et al., 2010]

Reviewer's note: this Reviewer concludes that there is not enough information to make any meaningful conclusion on the use of Epanova in pregnant and lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness in pediatric patients have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Sponsor stated that there have been no reports of overdose, drug abuse or dependence, withdrawal or rebound with Epanova.

7.7 Additional Submissions / Safety Issues

7.7.1 120-Day Safety Update

The 120-day safety update provided by the applicant included a literature search to identify reports relevant to the clinical safety of Epanova. This search included the period, October 2012 through October 2013 and the following terms: Epanova, omefas, omega-3 free-fatty acids (FFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and ethyl ester (EE) products. The following databases were searched: Medline, ToxFile, AGRICOLA, and Agris. A total of 24 published clinical trials of duration longer than 3 months were identified. These publications confirmed the previously known safety and tolerability profile of Epanova. No new safety concerns for the administration of EPA and/or DHA in the form of FFA, TG, or EE ranging from 3 months to five years were identified.

8 Postmarket Experience

As of April 28, 2014, Epanova had not been approved or licensed for use in any country.

9 Appendices

9.1 Literature Review/References

The applicant conducted a literature search for publications related to the safety of Epanova as part of the 120 Day Safety Update. The search covered the period from October 2012 through October 30, 2013 and used the following terms: Epanova, omefas, omega-3 free-fatty acids (FFA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and included ethyl ester (EE) products. The following databases were searched: Medline, ToxFile, AGRICOLA, and Agris. The applicant reported 24 studies in abstract form. These studies related to a variety of conditions and patient population including age-related macular degeneration, inflammatory markers in subjects with severe hypertriglyceridemia and in subjects with type 2 diabetes, gestation duration and infant size at birth, DHA supplementation in nursing mothers, perinatal depression, physical performances and bone mass in post-menopausal women, linear growth in infants, cognitive functions and mild cognitive impairment in young adults and in elderly subjects respectively, Alzheimer disease, Vitamin D levels in dialysis patients, and protection against the toxicity induced by the chemiotherapeutic agent paclitaxel. Based on this review update, no novel safety concerns became known.

The abstracts are listed below:

APPENDIX B: ABSTRACTS OF INDIVIDUAL PUBLICATIONS

Arnold et al JAMA Ophthalmol 2013

TITLE: Macular xanthophylls and ω -3 long-chain polyunsaturated fatty acids in age-related macular degeneration: a randomized trial.

AUTHOR(S): Arnold C, Winter L, Fröhlich K, Jentsch S, Dawczynski J, Jahreis G, Böhm V.

SOURCE: JAMA Ophthalmol. 2013 May;131(5):564-72.

AFFILIATION: Bioactive Plant Products Research Group, Institute of Nutrition, Friedrich Schiller University Jena, Jena, Germany.

ABSTRACT:

IMPORTANCE: It has been shown that the functionality of the macula lutea depends on the nutritional uptake of lutein and zeaxanthin and that it is inversely associated with the risk of age-related macular degeneration (AMD). Additionally, ω -3 long-chain polyunsaturated fatty acids (LC-PUFAs) may also be protective.

OBJECTIVE: To investigate the effect of a 12-month intervention with macular xanthophylls and ω -3 LC-PUFAs on xanthophylls and fatty acids in plasma, antioxidant capacity, and optical density of the macular pigment of patients with nonexudative AMD.

DESIGN: The LUTEGA study was a randomized, double-blind, placebo-controlled, parallel clinical trial that was conducted for 12 months.

SETTING: University Eye Hospital and Institute of Nutrition, Friedrich Schiller University Jena, Germany.

PARTICIPANTS: A total of 172 individuals with nonexudative AMD.

INTERVENTION: Individuals were enrolled and randomly divided as follows: placebo group, group 1 (a capsule containing 10 mg of lutein, 1 mg of zeaxanthin, 100 mg of docosahexaenoic acid, and 30 mg of eicosapentaenoic acid administered each day), and group 2 (same substances but twice the dose used in group 1). One hundred forty-five participants completed the study successfully.

MAIN OUTCOME MEASURES: Plasma xanthophyll concentrations and fatty acid profiles, optical density of the macular pigment, and antioxidant capacity in plasma (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid [Trolox] equivalent antioxidant capacity and photochemiluminescence).

RESULTS: The concentrations of the administered carotenoids in plasma as well as the optical density of the macular pigment increased significantly in the groups randomized to receive supplementary macular xanthophylls and ω -3 LC-PUFAs after 1 month of intervention and remained at this level through the end of the study. Use of the double dose resulted in a beneficial alteration of the fatty acid profile in the plasma of patients with AMD in comparison with the dose in group 1. The lipophilic antioxidant capacity in plasma was significantly elevated with the intervention.

CONCLUSIONS AND RELEVANCE: A supplement containing a fixed combination of lutein, zeaxanthin, and ω -3 LC-PUFAs during 12 months significantly improved plasma antioxidant capacity, circulating macular xanthophyll levels, and the optical density of the macular pigment.

PMID: 23519529

Bays et al Am J Cardiovasc Drugs 2013

TITLE: Icosapent ethyl, a pure ethyl ester of eicosapentaenoic acid: effects on circulating markers of inflammation from the MARINE and ANCHOR studies.

AUTHOR(S): Bays HE, Ballantyne CM, Braeckman RA, Stirtan WG, Soni PN.

SOURCE: Am J Cardiovasc Drugs. 2013 Feb;13(1):37-46.

AFFILIATION: Louisville Metabolic and Atherosclerosis Research Center, 3288 Illinois Avenue, Louisville, KY 40213, USA. HBaysMD@aol.com

ABSTRACT:

BACKGROUND: Icosapent ethyl (IPE) is a high-purity prescription form of eicosapentaenoic acid ethyl ester approved by the US Food and Drug Administration as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. In addition to TG-lowering effects, IPE also reduces non-high-density lipoprotein cholesterol and apolipoprotein B levels without significantly increasing low density lipoprotein cholesterol (LDL-C) in patients with very high TG levels ≥ 500 mg/dL (MARINE study) and in patients with well-controlled LDL-C and residually high TG levels 200-500 mg/dL (ANCHOR study). This analysis examined the effect of IPE on inflammatory markers in patients from MARINE and ANCHOR.

METHODS: MARINE (N = 229) and ANCHOR (N = 702) were Phase III, double-blind studies that randomized hypertriglyceridemic patients to IPE 4 g/day, 2 g/day, or placebo. This analysis assessed the median placebo-adjusted percentage change from baseline in markers representing various stages of atherosclerotic inflammation such as intercellular adhesion molecule-1 (ICAM-1), oxidized low-density lipoprotein (Ox-LDL), lipoprotein associated phospholipase A(2) (Lp-PLA(2)), interleukin-6 (IL-6), and high-sensitivity C-reactive protein (hsCRP).

RESULTS: Compared to placebo, IPE 4 g/day significantly decreased Ox-LDL (13 %, $p < 0.0001$, ANCHOR), Lp-PLA(2) (14 %, $p < 0.001$, MARINE; 19 %, $p < 0.0001$, ANCHOR), and hsCRP levels (36 %, $p < 0.01$, MARINE; 22 %, $p < 0.001$, ANCHOR), but did not significantly change ICAM-1 and IL-6 levels. In the MARINE study, IPE 2 g/day did not significantly change ICAM-1, Ox-LDL, Lp-PLA(2), IL-6, or hsCRP levels. Also, compared to placebo in the ANCHOR study, IPE 2 g/day significantly decreased Lp-PLA(2) levels (8 %, $p < 0.0001$), but did not significantly change levels of other assessed inflammatory markers.

CONCLUSION: Compared to placebo, in hypertriglyceridemic patients, IPE 4 g/day significantly decreased Ox-LDL, Lp-PLA(2), and hsCRP levels.

PMID: 23325450 PMCID: PMC3572383

Carlson et al Am J Clin Nutr 2013

TITLE: DHA supplementation and pregnancy outcomes.

AUTHOR(S): Carlson SE, Colombo J, Gajewski BJ, Gustafson KM, Mundy D, Yeast J, Georgieff MK, Markley LA, Kerling EH, Shaddy DJ.

SOURCE: Am J Clin Nutr. 2013 Apr;97(4):808-15.

AFFILIATION: Department of Dietetics and Nutrition, University of Kansas Medical Center, Kansas City, KS 66160, USA. scarlson@kumc.edu

ABSTRACT:

BACKGROUND: Observational studies associate higher intakes of n-3 (omega-3) long chain polyunsaturated fatty acids (LCPUFAs) during pregnancy with higher gestation duration and birth size. The results of randomized supplementation trials using various n-3 LCPUFA sources and amounts are mixed.

OBJECTIVE: We tested the hypothesis that 600 mg/d of the n-3 LCPUFA docosahexaenoic acid (DHA) can increase maternal and newborn DHA status, gestation duration, birth weight, and length. Safety was assessed.

DESIGN: This phase III, double-blind, randomized controlled trial was conducted between January 2006 and October 2011. Women (n = 350) consumed capsules (placebo, DHA) from <20 wk. of gestation to birth. Blood (enrollment, birth, and cord) was analyzed for red blood cell (RBC) phospholipid DHA. The statistical analysis was intent-to-treat.

RESULTS: Most of the capsules were consumed (76% placebo; 78% DHA); the mean DHA intake for the treated group was 469 mg/d. In comparison with placebo, DHA supplementation resulted in higher maternal and cord RBC-phospholipid-DHA (2.6%; $P < 0.001$), longer gestation duration (2.9 d; $P = 0.041$), and greater birth weight (172 g; $P = 0.004$), length (0.7 cm; $P = 0.022$), and head circumference (0.5 cm; $P = 0.012$). In

addition, the DHA group had fewer infants born at <34 wk. of gestation ($P = 0.025$) and shorter hospital stays for infants born preterm (40.8 compared with 8.9 d; $P = 0.026$) than did the placebo group. No safety concerns were identified.

CONCLUSIONS: A supplement of 600 mg DHA/d in the last half of gestation resulted in overall greater gestation duration and infant size. A reduction in early preterm and very-low birth weight could be important clinical and public health outcomes of DHA supplementation. This trial was registered at clinicaltrials.gov as NCT00266825. PMID: 23426033 PMID: PMC3607655

AREDS2 Group JAMA 2013

TITLE: Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.

AUTHOR(S): Age-Related Eye Disease Study 2 Research Group.

SOURCE: JAMA. 2013 May 15;309(19):2005-15.

AFFILIATION: Emily Y. Chew, MD, National Eye Institute, National Institutes of Health, Bldg 10, CRC Room 3-2531, 10 Center Dr, MSC 1204, Bethesda, MD 20892-1204 (echew@nei.nih.gov).

ABSTRACT:

IMPORTANCE: Oral supplementation with the Age-Related Eye Disease Study (AREDS) formulation (antioxidant vitamins C and E, beta carotene, and zinc) has been shown to reduce the risk of progression to advanced age-related macular degeneration (AMD). Observational data suggest that increased dietary intake of lutein + zeaxanthin (carotenoids), omega-3 long chain polyunsaturated fatty acids (docosahexaenoic acid [DHA] + eicosapentaenoic acid [EPA]), or both might further reduce this risk.

OBJECTIVES: To determine whether adding lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation decreases the risk of developing advanced AMD and to evaluate the effect of eliminating beta carotene, lowering zinc doses, or both in the AREDS formulation.

DESIGN, SETTING, AND PARTICIPANTS: The Age-Related Eye Disease Study 2 (AREDS2), a multicenter, randomized, double-masked, placebo-controlled phase 3 study with a 2 × 2 factorial design, conducted in 2006-2012 and enrolling 4203 participants aged 50 to 85 years at risk for progression to advanced AMD with bilateral large drusen or large drusen in 1 eye and advanced AMD in the fellow eye.

INTERVENTIONS: Participants were randomized to receive lutein (10 mg) + zeaxanthin (2 mg), DHA (350 mg) + EPA (650 mg), lutein + zeaxanthin and DHA + EPA, or placebo. All participants were also asked to take the original AREDS formulation or accept a secondary randomization to 4 variations of the AREDS formulation, including elimination of beta carotene, lowering of zinc dose, or both.

MAIN OUTCOMES AND MEASURES: Development of advanced AMD. The unit of analyses used was by eye.

RESULTS: Median follow-up was 5 years, with 1940 study eyes (1608 participants) progressing to advanced AMD. Kaplan-Meier probabilities of progression to advanced AMD by 5 years were 31% (493 eyes [406 participants]) for placebo, 29% (468 eyes

[399 participants]) for lutein + zeaxanthin, 31% (507 eyes [416 participants]) for DHA + EPA, and 30% (472 eyes [387 participants]) for lutein + zeaxanthin and DHA + EPA. Comparison with placebo in the primary analyses demonstrated no statistically significant reduction in progression to advanced AMD (hazard ratio [HR], 0.90 [98.7% CI, 0.76-1.07]; P = .12 for lutein + zeaxanthin; 0.97 [98.7% CI, 0.82-1.16]; P = .70 for DHA + EPA; 0.89 [98.7% CI, 0.75-1.06]; P = .10 for lutein + zeaxanthin and DHA + EPA). There was no apparent effect of beta carotene elimination or lower-dose zinc on progression to advanced AMD. More lung cancers were noted in the beta carotene vs. no beta carotene group (23 [2.0%] vs. 11 [0.9%], nominal P = .04), mostly in former smokers.

CONCLUSIONS AND RELEVANCE: Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD. However, because of potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00345176.

PMID: 23644932

García-Layana et al Nutrients 2013

TITLE: Effects of lutein and docosahexaenoic Acid supplementation on macular pigment optical density in a randomized controlled trial.

AUTHOR(S): García-Layana A, Recalde S, Alamán AS, Robredo PF.

SOURCE: Nutrients. 2013 Feb 15;5(2):543-51.

AFFILIATION: Ophthalmology Department, Clinica Universidad de Navarra, Pamplona, Spain. aglayana@unav.es

ABSTRACT:

We studied the macular pigment ocular density (MPOD) in patients with early age macular degeneration (AMD) before and 1 year after nutritional supplementation with lutein and docosahexaenoic acid (DHA). Forty-four patients with AMD were randomly divided into two groups that received placebo (n = 21) or a nutritional supplement (n = 23, 12 mg of lutein and 280 mg of DHA daily). Heterochromatic flicker photometry was used to determine the MPOD. At baseline, the MPOD in AMD patients with placebo was 0.286 ± 0.017 meanwhile in AMD patients with supplementation it was 0.291 ± 0.016 . One year later, the mean MPOD had increased by 0.059 in the placebo group and by 0.162 in patients receiving lutein and DHA. This difference between groups was significant ($p < 0.05$). Lutein and DHA supplementation is effective in increasing the MPOD and may aid in prevention of age related macular degeneration.

PMID: 23434908 PMID: PMC3635211

Hutchins-Wiese et al J Nutr Health Aging 2013

TITLE: The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants on physical performance in postmenopausal women.

AUTHOR(S): Hutchins-Wiese HL, Kleppinger A, Annis K, Liva E, Lammi-Keefe CJ, Durham HA, Kenny AM.

SOURCE: J Nutr Health Aging. 2013 Jan;17(1):76-80.

AFFILIATION: Center on Aging, MC-5215, University of Connecticut Health Center Farmington, CT 06030-5215, USA.

ABSTRACT:

OBJECTIVES: Identify relationships and evaluate effects of long chain polyunsaturated fatty acids (LCPUFA) on frailty and physical performance.

DESIGN: Randomized, double blind pilot study.

SETTING: University General Clinical Research Center.

PARTICIPANTS: 126 postmenopausal women.

INTERVENTION: 2 fish oil (1.2g eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) or 2 placebo (olive oil) capsules per day for 6 months. All participants received calcium and vitamin D supplements.

MEASUREMENTS: Fatty acid levels, frailty assessment, hand grip strength, 8 foot walk, body composition, medical history and co-morbidities, nutrient intake, and inflammatory biomarkers taken at baseline and 6 months.

RESULTS: At baseline, those with greater red blood cell (RBC) DHA and DHA/arachidonic acid (AA) presented with less frailty ($r = -0.242$, $p=0.007$ and $r = -0.254$, $p=0.004$, respectively). Fish oil supplementation resulted in higher RBC DHA and lower AA compared to baseline and placebo ($p<0.001$) and an improvement in walking speed compared to placebo (3.0 ± 16 vs. -3.5 ± 14 , $p=0.038$). A linear regression model included age, antioxidant intake (selenium and vitamin C), osteoarthritis, frailty phenotype, and tumor necrosis factor alpha (TNF α). The model explained 13.6% of the variance in the change in walking speed. Change in DHA/AA ($p=0.01$) and TNF α ($p=0.039$), and selenium intake ($p=0.031$) had the greatest contribution to change in walking speed.

CONCLUSION: Physical performance, measured by change in walking speed, was significantly affected by fish oil supplementation. Dietary intake of antioxidants (selenium

and vitamin C) and changes in TNF α also contributed to change in walking speed suggesting LCPUFA may interact with antioxidants and inflammatory response to impact physical performance.

PMID: 23299384

Labonté et al J Nutr Health Aging 2013

TITLE: Eicosapentaenoic and docosahexaenoic acid supplementation and inflammatory gene expression in the duodenum of obese patients with type 2 diabetes.

AUTHOR(S): Labonté ME, Couture P, Tremblay AJ, Hogue JC, Lemelin V, Lamarche B.

SOURCE: Nutr J. 2013 Jul 15;12(1):98.

AFFILIATION: Institute of Nutrition and Functional Foods, Laval University, 2440 boul.Hochelaga, Québec (Qc) G1V 0A6, Canada

benoit.lamarche@fsaa.ulaval.ca;

ABSTRACT:

BACKGROUND: The extent to which long-chain omega-3 polyunsaturated fatty acids (LCn-3PUFA) from fish oil such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) exert their anti-inflammatory effects by down-regulating intestinal inflammation in humans is unknown. We investigated the impact of LCn-3PUFA supplementation on inflammatory gene expression in the duodenum of obese patients with type 2 diabetes.

FINDINGS: This placebo-controlled randomized crossover study included 12 men with type 2 diabetes. After a 4-week run-in period, patients received in a random sequence 5 g/d of fish oil (providing 3 g of EPA + DHA) and a placebo (corn and soybean oil) for 8 weeks each. The two treatment phases were separated by a 12-week washout period. Gene expression was assessed by real-time polymerase chain reaction in duodenal biopsy samples obtained in the fasted state at the end of each treatment phase. Intestinal mRNA expression levels of interleukin (IL)-6 and tumor-necrosis factor (TNF)-alpha were hardly detectable after either treatment (<100 copies/105 copies of the reference gene ATP5o). Intestinal mRNA expression of IL-18 and of the transcription factor signal transducer and activator of transcription 3 (STAT3) was higher (<5000 copies/105 copies ATP5o) but still relatively low. EPA + DHA supplementation had no impact on any of these levels (all P >= 0.73).

CONCLUSIONS: These data suggest that duodenal cells gene expression of proinflammatory cytokines is low in patients with type 2 diabetes and not affected by EPA +DHA supplementation. Further studies are warranted to determine if inflammatory gene expression in other tissues surrounding the intestine is modulated by EPA + DHA supplementation. Trial registration: ClinicalTrials.gov ID: NCT01449773.

PMID: 23855973 PMCID: PMC3718629

Lappe et al Eur J Nutr 2013

TITLE: Effect of a combination of genistein, polyunsaturated fatty acids and vitamins D3 and K1 on bone mineral density in postmenopausal women: a randomized, placebo-controlled, double-blind pilot study.

AUTHOR(S): Lappe J, Kunz I, Bendik I, Prudence K, Weber P, Recker R, Heaney RP.

SOURCE: Eur J Nutr. 2013 Feb;52(1):203-215.

AFFILIATION: Osteoporosis Research Center, Creighton University Medical Center, 601 North 30th Street, Suite 4820, Omaha, NE 68131, USA.e-mail: jmlappe@creighton.edu

ABSTRACT:

PURPOSE: Many postmenopausal women desire non-pharmaceutical alternatives to hormone therapy for protection against osteoporosis. Soybean isoflavones, especially genistein, are being studied for this purpose. This study examined the effects of synthetic genistein in combination with other potential bone-protective dietary molecules on bone mineral density (BMD) in early postmenopausal women.

METHODS: In this 6-month double-blind pilot study, 70 subjects were randomized to

receive daily either calcium only or the geniVida™ bone blend (GBB), which consisted of genistein (30 mg/days), vitamin D3 (800 IU/days), vitamin K1 (150 µg/days) and polyunsaturated fatty acids (1 g polyunsaturated fatty acids as ethyl ester: eicosapentaenoic acid/docosahexaenoic acid ratio = ~2/1). Markers of bone resorption and formation and BMD at the femoral neck, lumbar spine, Ward's triangle, trochanter and intertrochanter, total hip and whole body were assessed.

RESULTS: Subjects supplemented with the GBB (n = 30) maintained femoral neck BMD, whereas in the placebo group (n = 28), BMD significantly decreased (p = 0.007). There was also a significant difference (p < 0.05) in BMD between the groups at Ward's triangle in favor of the GBB group. Bone-specific alkaline phosphatase and N-telopeptide significantly increased in the GBB group in comparison with those in baseline and in the placebo group. The GBB was well tolerated, and there were no significant differences in adverse events between groups.

CONCLUSIONS: The GBB may help to prevent osteoporosis and reduce fracture risk, at least at the hip, in postmenopausal women. Larger and longer-term clinical trials are warranted.

Lee et al Psychopharmacology (Berl) 2013

TITLE: Docosahexaenoic acid-concentrated fish oil supplementation in subjects with mild cognitive impairment (MCI): a 12-month randomised, double-blind, placebo-controlled trial.

AUTHOR(S): Lee LK, Shahar S, Chin AV, Yusoff NA.

SOURCE: Psychopharmacology (Berl). 2013 Feb;225(3):605-12.

AFFILIATION: Nutrition Science Program, School of Health Care Sciences, Faculty of Health Sciences, University Kebangsaan Malaysia, Kuala Lumpur, Malaysia.

ABSTRACT:

RATIONALE: Epidemiological studies have suggested a beneficial effect of fish oil supplementation in halting the initial progression of Alzheimer's disease. However, it remains unclear whether fish oil affects cognitive function in older people with mild cognitive impairment (MCI).

OBJECTIVES: This study investigated the effects of fish oil supplementation on cognitive function in elderly person with MCI.

METHODS: This was a 12-month, randomised, double-blind, placebo-controlled study using fish oil supplementation with concentrated docosahexaenoic acid (DHA). Thirty six low socioeconomic-status elderly subjects with MCI were randomly assigned to receive either concentrated DHA fish oil (n = 18) or placebo (n = 18) capsules. The changes of memory, psychomotor speed, executive function and attention, and visual-constructive skills were assessed using cognitive tests. Secondary outcomes were safety and tolerability of the DHA concentrate.

RESULTS: The fish oil group showed significant improvement in short-term and working memory (F = 9.890; ηp^2 (2) = 0.254; p < 0.0001), immediate verbal memory (F = 3.715; ηp^2 (2) = 0.114; p < 0.05) and delayed recall capability (F = 3.986; ηp^2 (2) = 0.121; p < 0.05). The 12-month change in memory (p < 0.01) was significantly

better in the fish oil group. Fish oil consumption was well tolerated, and the side effects were minimal and self-limiting.

CONCLUSIONS:

This study suggested the potential role of fish oil to improve memory function in MCI subjects. Studies with larger sample sizes, longer intervention periods, different fish oil dosages and genetic determinations should be investigated before definite recommendations can be made.

PMID: 22932777

Mi et al Nutrition 2013

TITLE: Nutritional approaches in the risk reduction and management of Alzheimer's disease.

AUTHOR(S): Mi W, van Wijk N, Cansev M, Sijben JW, Kamphuis PJ.

SOURCE: Nutrition. 2013 Sep;29(9):1080-9.

AFFILIATION: Nutricia Advanced Medical Nutrition, Danone Research, Centre for Specialised Nutrition, Wageningen, The Netherlands.

ABSTRACT:

Alzheimer's disease (AD) is a heterogeneous and devastating neurodegenerative disease with increasing socioeconomic burden for society. In the past 30 y, notwithstanding advances in the understanding of the pathogenesis of the disease and consequent development of therapeutic approaches to novel pathogenic targets, no cure has so far emerged. This contribution focuses on recent nutritional approaches in the risk reduction and management of AD with emphasis on factors providing a rationale for nutritional approaches in AD, including compromised nutritional status, altered nutrient uptake and metabolism, and nutrient requirements for synapse formation. Collectively these factors are believed to result in specific nutritional requirement in AD. The chapter also emphasizes investigated nutritional interventions in patients with AD, including studies with single nutrients and with the specific nutrient combination Fortasyn Connect and discusses the current shift of paradigm to intervene in earlier stages of AD, which offers opportunities for investigating nutritional strategies to reduce the risk for disease progression. Fortasyn Connect was designed to enhance synapse formation and function in AD by addressing the putative specific nutritional requirements and contains docosahexaenoic acid, eicosapentaenoic acid, uridine-5'-mono-phosphate, choline, phospholipids, antioxidants, and B vitamins. Two randomized controlled trials (RCTs) with the medical food Souvenaid, containing Fortasyn Connect, showed that this intervention improved memory performance in mild, drug-naïve patients with AD. Electroencephalography outcome in one of these clinical studies suggests that Souvenaid has an effect on brain functional connectivity, which is a derivative of changed synaptic activity. Thus, these studies suggest that nutritional requirements in AD can be successfully addressed and result in improvements in behavioral and neuro-physiological alterations that are characteristic to AD. The recent advance of methodologies and techniques for early diagnosis of AD facilitates the investigation of strategies to reduce the risk for AD progression in the earliest stages of the disease. Nutrition-based approaches deserve further investigation as an integral

part of such strategies due to their low risk for side effects and their potential to affect pathological processes of very early AD.

PMID: 23756280

Mozurkewich et al Am J Obstet Gynecol 2013

TITLE: The Mothers, Omega-3, and Mental Health Study: a double-blind, randomized controlled trial.

AUTHOR(S): Mozurkewich EL, Clinton CM, Chilimigras JL, Hamilton SE, Allbaugh LJ, Berman DR, Marcus SM, Romero VC, Treadwell MC, Keeton KL, Vahratian AM, Schrader RM, Ren J, Djuric Z.

SOURCE: Am J Obstet Gynecol. 2013 Apr;208(4):313.

AFFILIATION: Department of Obstetrics and Gynecology, University of Michigan Medical School, Ann Arbor, MI, USA.

ABSTRACT:

OBJECTIVES: Maternal deficiency of the omega-3 fatty acid, docosahexaenoic acid (DHA), has been associated with perinatal depression, but there is evidence that supplementation with eicosapentaenoic acid (EPA) may be more effective than DHA in treating depressive symptoms. This trial tested the relative effects of EPA- and DHA-rich fish oils on prevention of depressive symptoms among pregnant women at an increased risk of depression.

STUDY DESIGN: We enrolled 126 pregnant women at risk for depression (Edinburgh Postnatal Depression Scale score 9-19 or a history of depression) in early pregnancy and randomly assigned them to receive EPA-rich fish oil (1060 mg EPA plus 274 mg DHA), DHA-rich fish oil (900 mg DHA plus 180 mg EPA), or soy oil placebo. Subjects completed the Beck Depression Inventory (BDI) and Mini-International Neuropsychiatric Interview at enrollment, 26-28 weeks, 34-36 weeks, and at 6-8 weeks' postpartum. Serum fatty acids were analyzed at entry and at 34-36 weeks' gestation.

RESULTS: One hundred eighteen women completed the trial. There were no differences between groups in BDI scores or other depression endpoints at any of the 3 time points after supplementation. The EPA- and DHA-rich fish oil groups exhibited significantly increased post supplementation concentrations of serum EPA and serum DHA respectively. Serum DHA- concentrations at 34-36 weeks were inversely related to BDI scores in late pregnancy.

CONCLUSION: EPA-rich fish oil and DHA-rich fish oil supplementation did not prevent depressive symptoms during pregnancy or postpartum.

PMID: 23531328

Nicholson et al Food Funct 2013

TITLE: The role of marine n-3 fatty acids in improving cardiovascular health: a review.

AUTHOR(S): Nicholson T, Khademi H, Moghadasian MH.

SOURCE: Food Funct. 2013 Feb 26;4(3):357-65

AFFILIATION: St. Boniface Research Centre, 351 Tache Ave, Winnipeg, Manitoba, Canada R2H 2A6. umnichot@cc.umanitoba.ca

ABSTRACT:

Omega 3 polyunsaturated fatty acids (n-3 PUFA) have long been studied for their health benefits. In particular, marine n-3 PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been shown to possess cardiovascular protective qualities. However, there is conflicting evidence as to the mechanisms, effectiveness and doses required to observe these benefits. The objective of this review is to provide existing evidence as to the role of marine n-3 PUFA on cardiovascular health, as well as provide novel aspects to the current literature as of September 2012. Three large randomized clinical studies were reviewed to determine if there was an inverse association between n-3 fatty acid intake and CVD. There is strong evidence that the pharmaceutical grade n-3 fatty acid drug Lovaza, (previously Omacor) is effective in reducing triglyceride levels in humans. However, there are possible adverse reactions that need to be taken into account and caution should be used in treating certain populations. The Omega-3 Index is a promising novel biomarker for assessing long term EPA + DHA status in humans. Due to the originality of the Index, additional evidence is required to assess this as a tool for predicting CVD. Future research is needed to determine the individual effects of EPA and DHA for cardio-protection. PMID: 23325431

Offman et al Vasc Health Risk Manag 2013

TITLE: Steady-state bioavailability of prescription omega-3 on a low-fat diet is significantly improved with a free fatty acid formulation compared with an ethyl ester formulation: the ECLIPSE II study.

AUTHOR(S): Offman E, Marengo T, Ferber S, Johnson J, Kling D, Curcio D, Davidson M.

SOURCE: Vasc Health Risk Manag. 2013;9:563-73.

AFFILIATION: Clinical Pharmacology Sciences, Celerion, Montreal, QC, Canada.

ABSTRACT:

The systemic bioavailability of free fatty acid (FFA) forms of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compared with ethyl ester (EE) forms is dependent on the presence of intestinal lipases and is highest during consumption of high-fat meals. Given that patients with cardiovascular disease are advised to reduce dietary fat intake, potentially lowering the bioavailability and therapeutic benefit, the hypothesis that FFA forms provide for higher bioavailability compared with EE forms under low-fat diet conditions was tested where the pharmacokinetics of the FFA form (Epanova™) were compared with those of an ethyl ester form (Lovaza®) following repeat dosing. Fifty-two healthy male and female subjects were equally allocated to one of two open-label, parallel-group cohorts. Following a Therapeutic Lifestyle Changes diet for a minimum of 7 days, blood samples were drawn for endogenous values for EPA and DHA over a 24-hour period. Subjects were then administered 4 x 1 g capsules of either Epanova (OM3 FFA) or Lovaza (OM3 EE) once daily for 14 days, following which serial blood samples were drawn over a 24-hour period to characterize the bioavailability of EPA and DHA from the respective formulations. In addition, changes

from baseline in lipid profile were explored. Systemic bioavailability, as measured by area under the curve from time zero to 24 hours (AUC(0-τ)) and the maximum measured plasma concentrations during the 0-24 hour dosing interval (C(max,ss)) of unadjusted total plasma EPA + DHA were approximately 3-fold and 3.9-fold higher, respectively, for Epanova relative to Lovaza. Following baseline adjustment, the magnitude of difference in bioavailability was approximately 5.8-fold and 6.5-fold higher in AUC(0-τ) and C(max,ss), respectively, for Epanova relative to Lovaza. Serum triglycerides were reduced by a significantly greater extent (P = 0.013) for Epanova relative to Lovaza (21% versus 8%). The bioavailability of the FFA forms of EPA and DHA in Epanova are significantly greater than the bioavailability from the EE forms present in Lovaza under lowfat dietary conditions normally recommended for patients with cardiovascular disease. This increased bioavailability may lead to improved triglyceride-lowering in patients with hypertriglyceridemia.
PMID: 24124374 PMCID: PMC3794864

Souied et al Ophthalmology 2013

TITLE: Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study.

AUTHOR(S): Souied EH, Delcourt C, Querques G, Bassols A, Merle B, Zourdani A, Smith T, Benlian P; Nutritional AMD Treatment 2 Study Group.

SOURCE: Ophthalmology. 2013 Aug;120(8):1619-31

AFFILIATION: Ophthalmology Department, Hôpital Intercommunal de Créteil, University Paris Est Créteil, Créteil, France. eric.souied@chicreteil.fr

ABSTRACT:

OBJECTIVE: To evaluate the efficacy of docosahexaenoic acid (DHA)-enriched oral supplementation in preventing exudative age-related macular degeneration (AMD).

DESIGN: The Nutritional AMD Treatment 2 study was a randomized, placebo-controlled, double-blind, parallel, comparative study.

PARTICIPANTS: Two hundred sixty-three patients 55 years of age or older and younger than 85 years with early lesions of age-related maculopathy and visual acuity better than 0.4 logarithm of minimum angle of resolution units in the study eye and neovascular AMD in the fellow eye.

METHODS: Patients were assigned randomly to receive either 840 mg/day DHA and 270 mg/day eicosapentaenoic acid (EPA) from fish oil capsules or the placebo (olive oil capsules) for 3 years.

MAIN OUTCOME MEASURES: The primary outcome measure was time to occurrence of choroidal neovascularization (CNV) in the study eye. Secondary outcome measures in the study eye were: incidence of CNV developing in patients, changes in visual acuity, occurrence and progression of drusen, and changes in EPA plus DHA level in red blood cell membrane (RBCM).

RESULTS: Time to occurrence and incidence of CNV in the study eye were not significantly different between the DHA group (19.5±10.9 months and 28.4%, respectively) and the placebo group (18.7±10.6 months and 25.6%, respectively). In the DHA group, EPA plus DHA levels increased significantly in RBCM (+70%; P<0.001),

suggesting that DHA easily penetrated cells, but this occurred unexpectedly also in the placebo group (+9%; $P = 0.007$). In the DHA-allocated group, patients steadily achieving the highest tertile of EPA plus DHA levels in RBCM had significantly lower risk (-68%; $P = 0.047$; hazard ratio, 0.32; 95% confidence interval, 0.10-0.99) of CNV developing over 3 years. No marked changes from baseline in best-corrected visual acuity, drusen progression, or geographic atrophy in the study eye were observed throughout the study in either group.

CONCLUSIONS: In patients with unilateral exudative AMD, 3 years of oral DHA-enriched supplementation had the same effect on CNV incidence in the second eye as did the placebo. However, RBCM fatty acid measurements revealed that CNV incidence was significantly reduced in DHA-supplemented patients showing a steadily high EPA plus DHA index over 3 years.

PMID: 23395546

Stonehouse et al Am J Clin Nutr 2013

TITLE: DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial.

AUTHOR(S): Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, Kennedy D.

SOURCE: Am J Clin Nutr. 2013 May;97(5):1134-43.

AFFILIATION: Institute of Food, Nutrition and Human Health, Massey University, Auckland, New Zealand. w.stonehouse@massey.ac.nz

ABSTRACT:

BACKGROUND: Docosahexaenoic acid (DHA) is important for brain function, and its status is dependent on dietary intakes. Therefore, individuals who consume diets low in omega-3 (n-3) polyunsaturated fatty acids may cognitively benefit from DHA supplementation. Sex and apolipoprotein E genotype (APOE) affect cognition and may modulate the response to DHA supplementation.

OBJECTIVES: We investigated whether a DHA supplement improves cognitive performance in healthy young adults and whether sex and APOE modulate the response.

DESIGN: Healthy adults ($n = 176$; age range: 18-45 y; nonsmoking and with a low intake of DHA) completed a 6-mo randomized, placebo-controlled, double-blind intervention in which they consumed 1.16 g DHA/d or a placebo. Cognitive performance was assessed by using a computerized cognitive test battery. For all tests, z scores were calculated and clustered into cognitive domains as follows: episodic and working memory, attention, reaction time (RT) of episodic and working memory, and attention and processing speed. ANCOVA was conducted with sex and APOE as independent variables.

RESULTS: RTs of episodic and working memory improved with DHA compared with placebo [mean difference (95% CI): -0.18 SD (-0.33, -0.03 SD) ($P = 0.02$) and -0.36 SD (-0.58, -0.14 SD) ($P = 0.002$), respectively]. Sex \times treatment interactions occurred for episodic memory ($P = 0.006$) and the RT of working memory ($P = 0.03$). Compared with

the placebo, DHA improved episodic memory in women [0.28 SD (0.08, 0.48 SD); P = 0.006] and RTs of working memory in men [-0.60 SD (-0.95, -0.25 SD); P = 0.001]. APOE did not affect cognitive function, but there were some indications of APOE × sex × treatment interactions.

CONCLUSIONS: DHA supplementation improved memory and the RT of memory in healthy, young adults whose habitual diets were low in DHA. The response was modulated by sex. This trial was registered at the New Zealand Clinical Trials Registry (<http://www.anzctr.org.au/default.aspx>) as ACTRN12610000212055.
PMID: 23515006

Valentine et al Breastfeed Med 2013

TITLE: Randomized Controlled Trial of Docosahexaenoic Acid Supplementation in Midwestern U.S. Human Milk Donors

AUTHOR(S): Valentine CJ, Morrow G, Pennell M, Morrow AL, Hodge A, Haban-Bartz A, Collins K, Rogers LK.

SOURCE: Breastfeed Med. 2013 Feb;8(1):86-91.

AFFILIATION: University of Cincinnati Children's Hospital, Cincinnati, Ohio 45229, USA. Christina.valentine@cchmc.org

ABSTRACT:

BACKGROUND: Docosahexaenoic acid (DHA) is a long-chain polyunsaturated fatty acid important for neonatal neurodevelopment and immune homeostasis. Preterm infants fed donor milk from a Midwestern source receive only 20% of the intrauterine accretion of DHA. We tested the hypothesis that DHA supplementation of donor mothers would provide preterm infants with DHA intake equivalent to fetal accretion.

SUBJECTS AND METHODS: After Institutional Review Board approval and informed consent, human milk donors to the Mother's Milk Bank of Ohio were randomized to receive 1 g of DHA (Martek®) [now DSM Nutritional Lipids, Columbia, MD] or placebo soy oil. Dietary intake data were collected and analyzed by a registered dietitian. Fatty acids were measured by gas chromatography/flame ionization detection. Statistical analysis used linear mixed models.

RESULTS: Twenty-one mothers were randomly assigned to either the DHA group (n=10) or the placebo group (n=11). Donor age was a median of 31 years in both groups with a mean lactational stage of 19 weeks. Dietary intake of DHA at baseline in both groups was a median of 23 mg/day (range, 0-194 mg), significantly (p<0.0001) less than the minimum recommended intake of 200 mg/day. The DHA content of milk increased in the DHA supplemented group (p<0.05).

CONCLUSIONS: The women enrolled in this study had low dietary DHA intake. Supplementation with preformed DHA at 1 g/day resulted in increased DHA concentrations in the donor milk with no adverse outcomes. Infants fed donor milk from supplemented women receive dietary DHA levels that closely mimic normal intrauterine accretion during the third trimester.

PMID: 22568471 PMCID: PMC3566653

van der Merwe et al Am J Clin Nutr 2013

TITLE: Long-chain PUFA supplementation in rural African infants: a randomized controlled trial of effects on gut integrity, growth, and cognitive development.

AUTHOR(S): van der Merwe LF, Moore SE, Fulford AJ, Halliday KE, Drammeh S, Young S, Prentice AM.

SOURCE: Am J Clin Nutr. 2013 Jan;97(1):45-57.

AFFILIATION: Medical Research Council International Nutrition Group, London School of Hygiene and Tropical Medicine, London, United Kingdom.

ABSTRACT:

BACKGROUND: Intestinal damage and malabsorption caused by chronic environmental enteropathy are associated with growth faltering seen in infants in less-developed countries. Evidence has suggested that supplementary omega-3 (n-3) long-chain PUFAs (LC-PUFAs) might ameliorate this damage by reducing gastrointestinal inflammation. LC-PUFA supplementation may also benefit cognitive development.

OBJECTIVE: We tested whether early n-3 LC-PUFA supplementation improves infant intestinal integrity, growth, and cognitive function.

DESIGN: A randomized, double-blind, controlled trial [200 mg DHA and 300 mg EPA or 2 mL olive oil/d for 6 mo] was conducted in a population of 172 rural Gambian infants aged 3-9 mo. The primary endpoints were anthropometric measures and gut integrity [assessed by using urinary lactulose:mannitol ratios (LMRs)]. Plasma fatty acid status, intestinal mucosal inflammation (fecal calprotectin), daily morbidity, and cognitive development (2-step meansend test and an attention assessment) were secondary endpoints.

RESULTS: PUFA supplementation resulted in a significant increase in plasma n-3 LCPUFA concentrations ($P < 0.001$ for both DHA and EPA) and midupper arm circumference (MUAC) (effect size: 0.31 z scores; 95% CI: 0.06, 0.56; $P = 0.017$) at 9 mo of age. At 12 mo, MUAC remained greater in the intervention group, and we observed significant increases in skinfold thicknesses ($P \leq 0.022$ for all). No other significant differences between treatment groups were detected for growth or LMRs at 9 mo or for secondary outcomes.

CONCLUSIONS: Fish-oil supplementation successfully increased plasma n-3 fatty acid status. However, in young, breastfed Gambian infants, the intervention failed to improve linear growth, intestinal integrity, morbidity, or selected measures of cognitive development.

The trial was registered at www.isrctn.org as ISRCTN66645725.

PMID: 23221579 PMCID: PMC3522138

Alicandro et al Prostaglandins Leukot Essent Fatty Acids 2013

TITLE: A randomized placebo-controlled study on high-dose oral algal docosahexaenoic acid supplementation in children with cystic fibrosis.

AUTHOR(S): Alicandro G, Faelli N, Gagliardini R, Santini B, Magazzù G, Biffi A, Risé P, Galli C, Tirelli AS, Loi S, Valmarana L, Cirilli N, Palmas T, Vieni G, Bianchi ML, Agostoni C, Colombo C.

SOURCE: Prostaglandins Leukot Essent Fatty Acids. 2013 Feb;88(2):163-9.

AFFILIATION: Centro Fibrosi Cistica, Fondazione IRCCS Ca' Grande Ospedale Maggiore Policlinico, Università degli Studi di Milano, Italy.

ABSTRACT:

Low plasma concentrations of docosahexaenoic acid (DHA) are reported in unsupplemented cystic fibrosis (CF) patients. Forty-one CF patients aged from 6 to 12 years were randomized to receive high-dose DHA (100 mg/kg/day in the first month and 1g per day thereafter through a 12-month supplementation) or placebo (germ oil). Primary outcome was percentage change in plasma AA:DHA ratio. Secondary outcomes were changes in the number of pulmonary exacerbations compared to previous year, lung function, BMI, skinfold thicknesses, and body composition assessed by DXA and in serum concentrations of Creactive protein, cytokines and vitamin (α -tocopherol and retinol). Compared to the control group plasma AA:DHA ratio decreased in the intervention group after 6 months (median percentage changes: -73% in the intervention group vs. -10% in the control group, $P=0.001$). No differences were detected between groups for secondary outcomes. Despite a decrease of the AA/DHA ratio, DHA supplementation for one year did not induce any significant biochemical and clinical improvement in CF patients.
PMID: 23266209 [PubMed - indexed for MEDLINE]

An et al Nutr Res 2012

TITLE: Omega-3 fatty acid supplementation increases 1,25-dihydroxyvitamin D and fetuin-A levels in dialysis patients.

AUTHOR(S): An WS, Lee SM, Son YK, Kim SE, Kim KH, Han JY, Bae HR, Rha SH, Park Y.

SOURCE: Nutr Res. 2012 Jul;32(7):495-502.

AFFILIATION: Department of Internal Medicine, Dong-A University, 3Ga-1, Dongdaesin-Dong, Seo-Gu, Busan 602-715, Republic of Korea.
anws@dau.ac.kr

ABSTRACT:

Vitamin D deficiency, low levels of fetuin-A, and fibroblast growth factor 23 (FGF-23) are related to vascular calcification, which is associated with cardiovascular disease. We hypothesized that omega-3 fatty acid (FA), which has cardioprotective properties, modifies vitamin D status, fetuin-A, and FGF-23 levels in dialysis patients. In a randomized, open label, controlled study, a total of 47 patients treated with dialysis for at least 1 year were randomized to treatment for 6 months with omega-3 FAs (Omacor, 3 g/d; Pronova, Sandefjord, Norway) or a control group. Levels of fetuin-A and FGF-23 were measured by enzyme-linked immunoassay, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were measured by radioimmunoassay. The mean age of the enrolled patients was 57.4 ± 10.4 years, and mean dialysis duration was 46.5 ± 28.1 months. Twenty-seven hemodialysis patients and 16 peritoneal dialysis patients finished this trial. After 6 months, the levels of 1,25-dihydroxyvitamin D and fetuin-A were significantly increased in the group taking the omega-3 FA supplement compared with baseline. Levels of calcium, phosphorous, parathyroid hormone, 25-hydroxyvitamin D, FGF-23, and lipid profiles were not significantly changed in the omega-3 FA-

supplemented group after 6 months compared with baseline. The erythrocyte membrane contents of eicosapentaenoic acid and docosahexaenoic acid were significantly increased, and oleic acid content was significantly decreased in the omega-3 FA-supplemented group after 6 months compared with baseline. Regarding vascular calcification and cardiovascular disease, omega-3 FA supplementation may have a clinical benefit caused by activating vitamin D, increasing fetuin-A levels, and modifying erythrocyte membrane FA contents in dialysis patients. PMID: 22901557

Davidson et al J Clin Lipidol 2012

TITLE: A novel omega-3 free fatty acid formulation has dramatically improved bioavailability during a low-fat diet compared with omega-3-acid ethyl esters: the ECLIPSE (Epanova® compared to Lovaza® in a pharmacokinetic single-dose evaluation) study.

AUTHOR(S): Davidson MH, Johnson J, Rooney MW, Kyle ML, Kling DF.

SOURCE: J Clin Lipidol. 2012 Nov-Dec;6(6):573-84.

AFFILIATION: Omthera Pharmaceuticals, Inc., Princeton, NJ 08540, USA.
mdavidson@omthera.com

ABSTRACT:

BACKGROUND: Omega-3 (OM-3) fatty acid products are indicated for the treatment of severe hypertriglyceridemia; however, the omega-3-acid ethyl ester (OM-3 EE) formulations require significant pancreatic lipase stimulation with high-fat meals for adequate intestinal absorption of the metabolites eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A novel omega-3 free fatty acid (OM-3 FFA) formulation (Epanova®), Omthera Pharmaceuticals Inc., Princeton, NJ) was developed to maximize EPA and DHA bioavailability during a low-fat diet.

OBJECTIVE: To compare the relative bioavailability of EPA and DHA from single 4-gram doses of OM-3 FFA and a prescription OM-3 EE (Lovaza®), GlaxoSmithKline, Research Triangle Park, NC).

METHODS: This was a randomized, open-label, single dose, 4-way crossover, bioavailability study of OM-3 FFA and OM-3 EE administered during periods of low-fat and high-fat consumption to 54 overweight adults. Bioavailability was determined by the Intransformed area under the plasma concentration versus time curve (AUC(0-t)) during a 24-hour interval for EPA and DHA (baseline-adjusted).

RESULTS: The baseline-adjusted AUC(0-t) for total EPA + DHA during the low-fat period was 4.0-fold greater with OM-3 FFA compared with OM-3 EE (2650.2 vs. 662.0 nmol·h/mL, respectively; $P < .0001$). During the high-fat period, AUC(0-t) for OM-3 FFA was approximately 1.3-fold greater than OM-3 EE ($P < .0001$). During the low-fat period, 30 of 51 (58.8%) subjects dosed with OM-3 FFA maintained an AUC(0-t) that was $\geq 50\%$ of the respective high-fat AUC(0-t) in contrast to only 3 of 50 (6.0%) subjects dosed with OM-3 EE.

CONCLUSIONS: During a low-fat consumption period, the OM-3 FFA formulation provided dramatically improved bioavailability over the OM-3 EE formulation in overweight subjects. These findings offer a potential therapeutic advantage of the OM-3

FFA formulation for the treatment of severe hypertriglyceridemia as these patients are expected to adhere to a low-fat diet.

PMID: 23312053 [PubMed - indexed for MEDLINE]

Derosa et al J Clin Lipidol 2012

TITLE: Effects of n-3 PUFAs on postprandial variation of metalloproteinases, and inflammatory and insulin resistance parameters in dyslipidemic patients: evaluation with euglycemic clamp and oral fat load.

AUTHOR(S): Derosa G, Cicero AF, Fogari E, D'Angelo A, Bonaventura A, Romano D, Maffioli P.

SOURCE: J Clin Lipidol. 2012 Nov-Dec;6(6):553-64.

AFFILIATION: Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy. giuseppe.derosa@unipv.it

ABSTRACT:

BACKGROUND: The oral fat load (OFL) is considered as one of the most accurate models of postprandial lipoprotein metabolism and it has been widely used to evaluate the postprandial fat load effect on single markers of inflammation.

OBJECTIVE: To evaluate the effects of n-3 PUFAs, primarily eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with a content of 400 mg of EPA and 450 mg of DHA in each capsule, on metalloproteinases and inflammatory biomarkers in patients affected by combined dyslipidemia both in a fasting state and after a standardized OFL in a randomized, placebo-controlled trial.

METHODS: Placebo or n-3 PUFAs 3 g/day (1 g three times a day during the meals) was administered for 6 months. At the baseline, and after 2, 4, and 6 months we evaluated body mass index (BMI), body weight, fasting plasma glucose (FPG), fasting plasma insulin (FPI), homeostasis model assessment insulin resistance index (HOMA-IR), blood pressure, lipid profile, soluble intercellular adhesion molecule-1 (sICAM-1), interleukin 6 (IL-6), high sensitivity C-reactive protein (hs-CRP), soluble vascular cell adhesion molecule-1 (sVCAM-1), sE-selectin, tumor necrosis factor- α (TNF- α), and metalloproteinases 2 and 9 (MMP-2 and 9). Furthermore, at the baseline and at the end of the study, all patients underwent an euglycemic hyperinsulinemic clamp and an oral fat load.

RESULTS: Tg levels were lower (-54 mg/dL) and high-density lipoprotein cholesterol higher (+6 mg/dL) with n-3 PUFAs compared with placebo; n-3 PUFAs gave lower levels of FPG (-3 mg/dL), sICAM (-25 ng/mL), IL-6 (-0.3 pg/mL), hs-CRP (-0.6 mg/L), sVCAM-1 (-89 ng/mL), sE-selectin (-5.8 ng/mL), TNF- α (-0.3 ng/mL), MMP-2 (-185.1 ng/mL), and MMP-9 (-91.5 ng/mL), and a greater M value (+1.21 μ mol/min/kg) compared with placebo. After the OFL, there was a decrease of Tg, MMPs, and all inflammatory parameters with n-3 PUFAs, but not with placebo.

CONCLUSION: Supplementation with n-3 PUFA resulted in lower levels of FPG, plasma lipids, MMPs, and inflammatory parameters and in a better increase of M value compared to placebo, both in the fasting state and after an OFL.

PMID: 23312051

Ghoreishi et al BMC Cancer 2012

TITLE: Omega-3 fatty acids are protective against paclitaxel-induced peripheral neuropathy: a randomized double-blind placebo controlled trial.

AUTHOR(S): Ghoreishi Z, Esfahani A, Djazayeri A, Djalali M, Golestan B, Ayromlou H, Hashemzade S, Asghari Jafarabadi M, Montazeri V, Keshavarz SA, Darabi M.

SOURCE: BMC Cancer. 2012 Aug 15;12:355.

AFFILIATION: Department of Nutrition and Biochemistry, School of Health, Tehran University of Medical Sciences, Tehran, Iran.

ABSTRACT:

BACKGROUND: Axonal sensory peripheral neuropathy is the major dose-limiting side effect of paclitaxel. Omega-3 fatty acids have beneficial effects on neurological disorders from their effects on neurons cells and inhibition of the formation of proinflammatory cytokines involved in peripheral neuropathy.

METHODS: This study was a randomized double blind placebo controlled trial to investigate the efficacy of omega-3 fatty acids in reducing incidence and severity of paclitaxel-induced peripheral neuropathy (PIPn). Eligible patients with breast cancer randomly assigned to take omega-3 fatty acid pearls, 640 mg t.i.d during chemotherapy with paclitaxel and one month after the end of the treatment or placebo. Clinical and electrophysiological studies were performed before the onset of chemotherapy and one month after cessation of therapy to evaluate PIPn based on "reduced Total Neuropathy Score".

RESULTS: Twenty one patients (70%) of the group taking omega-3 fatty acid supplement (n= 30) did not develop PN while it was 40.7% (11 patients) in the placebo group (n = 27). A significant difference was seen in PN incidence (OR = 0.3, .95% CI = (0.10-0.88), p =0.029). There was a non-significant trend for differences of PIPn severity between the two study groups but the frequencies of PN in all scoring categories were higher in the placebo group (0.95% CI = (-2.06 -0.02), p = 0.054).

CONCLUSIONS: Omega-3 fatty acids may be an efficient neuroprotective agent for prophylaxis against PIPn. Patients with breast cancer have a longer disease free survival rate with the aid of therapeutical agents. Finding a way to solve the disabling effects of PIPn would significantly improve the patients' quality of life.

This trial was registered at ClinicalTrials.gov (NCT01049295).

PMID: 22894640 PMCID: PMC3459710

Milte et al Nutrition 2012

TITLE: Eicosapentaenoic and docosahexaenoic acids, cognition, and behavior in children with attention-deficit/hyperactivity disorder: a randomized controlled trial.

AUTHOR(S): Milte CM, Parletta N, Buckley JD, Coates AM, Young RM, Howe PR.

SOURCE: Nutrition. 2012 Jun;28(6):670-7.

AFFILIATION: Nutritional Physiology Research Centre, University of South Australia, Adelaide, South Australia, Australia.

ABSTRACT:

OBJECTIVE: To determine the effects of an eicosapentaenoic acid (EPA)-rich oil and a docosahexaenoic acid (DHA)-rich oil versus an ω -6 polyunsaturated fatty acid-rich safflower oil (control) on literacy and behavior in children with attention-deficit/hyperactivity disorder (ADHD) in a randomized controlled trial.

METHODS: Supplements rich in EPA, DHA, or safflower oil were randomly allocated for 4 mo to 90 Australian children 7 to 12 y old with ADHD symptoms higher than the 90th percentile on the Conners Rating Scales. The effect of supplementation on cognition, literacy, and parent-rated behavior was assessed by linear mixed modeling. Pearson correlations determined associations between the changes in outcome measurements and the erythrocyte fatty acid content (percentage of total) from baseline to 4 mo.

RESULTS: There were no significant differences between the supplement groups in the primary outcomes after 4 mo. However, the erythrocyte fatty acid profiles indicated that an increased proportion of DHA was associated with improved word reading ($r = 0.394$) and lower parent ratings of oppositional behavior ($r = 0.392$). These effects were more evident in a subgroup of 17 children with learning difficulties: an increased erythrocyte DHA was associated with improved word reading ($r = 0.683$), improved spelling ($r = 0.556$), an improved ability to divide attention ($r = 0.676$), and lower parent ratings of oppositional behavior ($r = 0.777$), hyperactivity ($r = 0.702$), restlessness ($r = 0.705$), and overall ADHD symptoms ($r = 0.665$).

CONCLUSION: Increases in erythrocyte ω -3 polyunsaturated fatty acids, specifically DHA, may improve literacy and behavior in children with ADHD. The greatest benefit may be observed in children who have comorbid learning difficulties.

PMID: 22541055

Richardson et al PLoS One 2012

TITLE: Docosahexaenoic acid for reading, cognition and behavior in children aged 7-9 years: a randomized, controlled trial (the DOLAB Study).

AUTHOR(S): Richardson AJ, Burton JR, Sewell RP, Spreckelsen TF, Montgomery P.

SOURCE: PLoS One. 2012;7(9):e43909.

AFFILIATION: Centre for Evidence-Based Intervention, University of Oxford, Oxford, United Kingdom. alex.richardson@spi.ox.ac.uk

ABSTRACT:

BACKGROUND: Omega-3 fatty acids are dietary essentials, and the current low intakes in most modern developed countries are believed to contribute to a wide variety of physical and mental health problems. Evidence from clinical trials indicates that dietary supplementation with long-chain omega-3 may improve child behavior and learning, although most previous trials have involved children with neurodevelopmental disorders such as attention deficit/hyperactivity disorder (ADHD) or developmental coordination disorder (DCD). Here we investigated whether such benefits might extend to the general child population.

OBJECTIVES: To determine the effects of dietary supplementation with the long-chain omega-3 docosahexaenoic acid (DHA) on the reading, working memory, and behavior of healthy schoolchildren.

DESIGN: Parallel group, fixed-dose, randomized, double-blind, placebo-controlled trial

(RCT).

SETTING: Mainstream primary schools in Oxfordshire, UK (n = 74).

PARTICIPANTS: Healthy children aged 7-9 years initially underperforming in reading (\leq 33rd centile). 1376 invited, 362 met study criteria.

INTERVENTION: 600 mg/day DHA (from algal oil), or taste/color matched corn/soybean oil placebo.

MAIN OUTCOME MEASURES: Age-standardized measures of reading, working memory, and parent- and teacher-rated behavior.

RESULTS: ITT analyses showed no effect of DHA on reading in the full sample, but significant effects in the pre-planned subgroup of 224 children whose initial reading performance was \leq 20th centile (the target population in our original study design). Parent-rated behavior problems (ADHD-type symptoms) were significantly reduced by active treatment, but little or no effects were seen for either teacher-rated behavior or working memory.

CONCLUSIONS: DHA supplementation appears to offer a safe and effective way to improve reading and behavior in healthy but underperforming children from mainstream schools. Replication studies are clearly warranted, as such children are known to be at risk of low educational and occupational outcomes in later life.

ClinicalTrials.gov NCT01066182 and Controlled-Trials.com ISRCTN99771026.

PMID: 22970149 PMCID: PMC3435388

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/s/

GIOVANNI CIZZA
05/02/2014

JAMES P SMITH
05/02/2014
Concur with recommended regulatory action.

CLINICAL FILING CHECKLIST FOR NDA 205060

NDA 205060
Epanova (omefas)
Applicant: Omthera Pharmaceuticals
Reviewers: Iffat N. Chowdhury, MD
(efficacy) and Giovanni Cizza, MD
(safety)

Filing Meeting: August 29, 2013
Date Received: July 05, 2013
PDUFA date: May 01, 2014

The applicant, Omthera Pharmaceuticals, Inc., has submitted NDA 205060 as a 505(b)(1) application for the following indication:

“Epanova (omefas) is indicated as an adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.”

According to the applicant, Epanova is a coated soft gelatin capsule containing a complex mixture of polyunsaturated free fatty acids derived from fish oils with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids.

Omefas contains not less than 85% (w/w) PUFA content of which approximately 550 mg/g is EPA and approximately 200 mg/g is DHA. The sum of the EPA and DHA content is approximately 750 mg/g. The total amount of omega-3 free fatty acids is not less than 800 mg/g. The total amount of total omega-6 free fatty acids is not more than (b) (4)%. Omefas also contains other minor components, including monounsaturated and saturated free fatty acids. It contains NMT (b) (4)% (a/a) monounsaturated and NMT (b) (4)% (a/a) saturated fatty acids.

Parameter	Ranges
Polyunsaturated free fatty acids	NLT 850 mg/g
<i>EPA</i>	500 to 600 mg/g
<i>DHA</i>	150 to 250 mg/g
<i>DPA</i>	(b) (4) mg/g
<i>EPA + DHA</i>	(b) (4) mg/g
<i>Total omega-3 fatty acids^a</i>	(b) (4) mg/g
<i>Total omega-6 fatty acids^b (a/a)</i>	NMT (b) (4) mg/g
<i>Other polyunsaturated fatty acids (a/a)</i>	NMT (b) (4) mg/g
Monounsaturated free fatty acids (a/a)	NMT (b) (4)%
Saturated free fatty acids (a/a)	NMT (b) (4)%

CLINICAL FILING CHECKLIST FOR NDA 205060

Apparently, the free fatty acids in Epanova do not depend on pancreatic lipase hydrolysis for transport and are readily absorbed. Hence, a central hypothesis of the Epanova clinical development program is that the comparatively greater bioavailability of the free fatty acids over the ethyl ester formulations could result in an acceptable efficacy at a lower dose per day (b) (4)

The recommended dosing provides (b) (4) 2 g or 4 g/day, (b) (4) (b) (4) as needed to effectively treat patients with severe hypertriglyceridemia (TG \geq 500 mg/dL).

This NDA is comprised of the following clinical trials:

- Study OM-EPA-003 (EVOLVE) for patients with fasting TG levels between 500 mg/dL and 2000 mg/dL
- Study OM-EPA-004 (ESPRIT) for patients with TG between 200 and 500 mg/dL despite statin therapy
- additional safety data in Crohn's disease patients under IND (b) (4) (EPIC-1, EPIC-2, EPIC-3 and EPIC-1E)
- Study OM-EPA-001: compares the bioavailability of EPA and DHA in fed and fasting states
- Study OM-EPA-006: PK/PD study with warfarin
- Study OM-EPA-007: PK study with simvastatin

Omthera submitted documentation in support of New Molecular Entity (NME) status for Epanova to IND 107,616 on February 15, 2013. However, a decision on the NME status is pending as of the date of the submission of this NDA.

The proposed established name, omefas, has been submitted to the USAN Council for approval. The request for review of the proprietary name, Epanova, will be submitted to this NDA as an amendment following the submission of the original application.

Exclusivity

The applicant requested 5 year exclusivity for Epanova on the basis of a "single active drug substance called omefas". According to the applicant, there has not been a drug approved containing the active moiety for which Omthera is seeking approval.

Pediatric Use

The applicant submitted a request for full waiver for pediatric studies for all pediatric age groups. The justification for this request is that due to the small number of pediatric patients with severe hypertriglyceridemia (TG >500 mg/dL), the necessary trials would be impossible or highly impracticable to conduct.

User Fee

The payment of the user fee for NDA 205060 (User Fee ID Number 3013461) in the amount of \$1,958,800 was provided via wire transfer on June 26, 2013.

CLINICAL FILING CHECKLIST FOR NDA 205060

Assessment

From a clinical standpoint, the NDA is fileable.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Pool A – safety data pooled from Study 003 and 004; Pool B safety data pooled from the Crohn’s studies
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?		X		One pivotal study, one supporting study in 2 different populations, so no ISE submitted.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			This is a 505(b)(1) application.
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			Pivotal study was conducted with 3 different doses compared to placebo
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the	X			

CLINICAL FILING CHECKLIST FOR NDA 205060

	Content Parameter	Yes	No	NA	Comment
	Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			In lieu of conducting a thorough QTc study, it was agreed that ECG assessment pre-dose and during periods of trough levels after dosing with Epanova was acceptable.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA 205060

	Content Parameter	Yes	No	NA	Comment
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant submitted a waiver for pediatric population
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

74-Day Letter Request- Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

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/s/

IFFAT N CHOWDHURY
08/30/2013

JAMES P SMITH
09/03/2013