

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205060Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	05 May 2014
<b>From</b>	James P. Smith, MD, MS
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA#</b>	205060
<b>Applicant</b>	AstraZeneca Pharmaceuticals LP (AstraZeneca); (Changed from Omthera Pharmaceuticals on 25 Feb 2014)
<b>Date of Submission</b>	05 July 2013
<b>PDUFA Goal Date</b>	05 May 2014
<b>Proprietary Name / Established (USAN) names</b>	EPANOVA / omega-3-carboxylic acids (formerly, omefas)
<b>Dosage forms / Strength</b>	Capsule / 1 gram
<b>Proposed Indication</b>	Severe hypertriglyceridemia
<b>Recommended:</b>	Approval

Material Reviewed/Consulted		
Medical Officer Review – Efficacy	03 May 2014	Iffat Chowdhury, MD
Medical Officer Review – Safety	02 May 2014	Giovanni Cizza, MD, PhD, MHSc
Statistical Review	16 Apr 2014	Cynthia Liu, MA
Clinical Pharmacology Review	27 Mar 2014	Suryanarayana Sista, PhD
QT-IRT Consult	16 Dec 2013	QT-IRT
CMC Review	27 Mar 2014	Martin Haber, PhD, and Xavier Ysern, PhD
Biopharmaceutics Review	26 Mar 2014	Houda Mahayni, PhD
Microbiology Review	19 Jul 2013	Bryant Riley, PhD
Pharmacology/Toxicology Review	28 Mar 2014	Parvaneh Espandiari, PhD
Clinical Inspection Summary/OSI	10 Apr 2014	Cynthia Kleppinger, MD
OSE/DMEPA Labeling Consult	30 Jan 2014	Michelle Rutledge, PharmD
OSE/DMEPA Proprietary Name Review	18 Sep 2013	Reasol Agustin, PharmD
OPDP Labeling Consult	08 Apr 2014	Ankur Kalola, PharmD
DMPP/OPDP Patient Package Insert Review	14 Apr 2014	Robin Duer, MBA, BSN, RN (DMPP), and Ankur Kalola, PharmD (OPDP)

QT-IRT: QT Interdisciplinary Review Team; CMC: Chemistry, Manufacturing, and Controls; OSI: Office of Scientific Investigations; OSE: Office of Surveillance and Epidemiology; DMEPA: Division of Medication Error Prevention and Analysis; OPDP: Office of Prescription Drug Promotion; DMPP: Division of Medical Policy Programs

### 1. INTRODUCTION

Omthera Pharmaceuticals (now, AstraZeneca) submitted a 505(b)(1) application for omega-3-carboxylic acids (formerly, omefas), tradename Epanova, seeking an indication as an adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia. The (b) (4) dosage of Epanova is 2 grams per day, (b) (4) (b) (4) 4 grams per day. Epanova would be available as 1-gram capsules.

If Epanova is approved, it would join three other prescription fish oil-derived products, all indicated for severe hypertriglyceridemia. According to data obtained from NHANES 1999-2004, approximately 1.7% of the U.S. population has TG  $\geq$ 500 mg/dL, or approximately 5 million individuals.<sup>1</sup> Lovaza (omega-3-acid ethyl esters) was approved in 2004 at a daily dose of 4 grams; Vascepa (icosapent ethyl) was approved in 2012 at a daily dose of 4 grams; and Omtryg (omega-3-acid ethyl esters A) was approved in 2014 at a daily dose of 4 grams. Other products currently available for the indication of severe hypertriglyceridemia include niacin-containing products and fibrates. Demonstration of an effect on serum triglycerides has historically been accepted by the Agency as the basis for approval for drugs indicated for severe ( $\geq$ 500 mg/dL) hypertriglyceridemia, where the primary rationale for treatment is believed to be the reduction of risk for acute pancreatitis, which even in this population, is a rare enough event to preclude trials powered for clinical outcomes.

Epanova capsules contain a complex mixture of polyunsaturated fatty acids (PUFAs), predominantly the omega-3 acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Unlike other fish oil-derived products currently on the market, the PUFAs that compose Epanova are in the fatty acid form (carboxylic acids) as opposed to ethyl esters (Lovaza, Vascepa, and Omtryg). The applicant emphasizes this difference between their product and Lovaza, given the greater bioavailability of Epanova.

There were no disagreements between primary reviewers regarding the approvability of this application; all have recommended approval.

## 2. BACKGROUND

IND 107616 was submitted on 25 March 2010 for the indication of severe hypertriglyceridemia; Epanova had been previously investigated for the treatment of Crohn's Disease under IND (b) (4) in the Division of Gastroenterology Products. An end-of-phase 2 (EOP2) meeting was held on 02 June 2010. Regarding the indication under consideration at this time, a special protocol assessment (SPA) for the single phase 3 trial OM-EPA-003 (also known as "EVOLVE") was submitted 02 July 2010 and ultimately agreed upon, after amendments, on 22 October 2010. On 25 April 2012, the applicant proposed an alternative to conducting a thorough QTc study by assessing ECGs recorded during OM-EPA-003; this was found acceptable.

A clinical pre-NDA meeting was held on 14 November 2012. The nonclinical development strategy was found reasonable. A clinical package containing OM-EPA-003 (pivotal) and OM-EPA-004 (a 6-week phase 3 trial (b) (4)), with long-term safety supported by data

<sup>1</sup> Ford E, et al. Hypertriglyceridemia and its pharmacologic treatment among US adults. *Arch Intern Med* 2009; 169:572-8.

from the former Crohn's disease program ("EPIC" trials), was found adequate for submission. Agreement was reached regarding the clinical pharmacology portion of the submission. Details regarding data pooling for the Integrated Summary of Safety (ISS) were found acceptable.

### 3. CMC

#### Drug Substance & Drug Product

Chemistry, manufacturing, and controls data related to both the drug substance (omega-3-carboxylic acids) and drug product (Epanova Capsules 1 g) are detailed in the review by Martin Haber, PhD, and Xavier Ysern, PhD. They recommend the NDA for approval. There are no pending CMC issues.

The drug substance (b) (4) at sites in Nova Scotia and Prince Edward Island, Canada, from crude fish oil obtained from (b) (4) fish (b) (4). It is a complex mixture of PUFAs, predominantly the omega-3 acids EPA (55%), DHA (20%), and docosapentaenoic acid (b) (4)%. It consistently contains (b) (4) omega-3 and (b) (4) omega-6 PUFA components: total omega-3 fatty acids are limited to not less than (b) (4)% and total omega-6 fatty acids are limited to not more than (b) (4)%. The drug substance also contains 0.3% (m/m)  $\alpha$ -tocopherol as (b) (4). During purification, (b) (4). Environmental pollutants (heavy metals, pesticides, (b) (4)) are controlled by specific tests on the drug substance (b) (4). Drug substance specifications include tests for acid value, saponification value, ester value, peroxide value, p-anisidine value, total oxidation value, cholesterol, oligomers, (b) (4), fatty acid composition (PUFAs, EPA, DHA, DPA, total omega-3 fatty acids, total omega-6 fatty acids, other polyunsaturated fatty acids, (b) (4)).

As described in the review by Drs. Haber and Ysern, the qualitative identify of the drug substance was developed by examining consistencies of peak patterns across 21 discrete lots: there are (b) (4) omega-3 and (b) (4) omega-6 PUFA peaks consistently present in the GC chromatograms (although not necessarily always above the limit of quantitation), which can be used to establish the fingerprint identity of omega-3-carboxylic acids (b) (4). The quantitative fatty acid composition is given in the table below, excerpted from p. 25 of their review:

**Table S.3.1-2. Fatty Acid Composition Acceptance Criteria for Drug Substance**

<i>Parameter</i>	<i>Ranges</i>
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<sup>a</sup></i>	(b) (4) mg/g
<i>Total omega-6 fatty acids<sup>b</sup> (a/a)</i>	NMT (b) (4) mg/g
<i>Other polyunsaturated fatty acids (a/a)</i>	NMT (b) (4) mg/g
<i>Monounsaturated free fatty acids (a/a)</i>	NMT (b) (4) %
<i>Saturated free fatty acids (a/a)</i>	NMT (b) (4) %

(b) (4)

In their review, Drs. Haber and Ysern comment (p. 44) that the omega-3 free fatty acids are in greatest abundance ((b) (4) %), with omega-6 free fatty acids contributing (b) (4) %, and all other free fatty acids each contributing less than (b) (4) % with the exception of (b) (4) ((b) (4) %) and (b) (4) ((b) (4) %). Notably, there are only quantitative requirements for EPA, DHA, total EPA+DHA, and total amount of omega-3 fatty acids.

The drug product is a soft gelatin oblong capsule containing 1000 mg (1 g) of the omega-3-carboxylic acids drug substance, (b) (4), and coated with a pigmented polymeric coat. The capsule gel, capsule coating, and printing ink components meet compendial requirements. The manufacturing method is a conventional process. Drug product specifications include identity tests (appearance by visual inspection and identification by GC), purity tests (acid value, peroxide value, p-anisidine value, total oxidation value, and Absorbance), strength tests (polyunsaturated free fatty acids content, EPA content, DHA content, EPA plus DHA content, and total omega-3 content), quality tests (uniformity of mass of single dose, average mass of contents, average mass of capsules, oligomers content, total glycerides content,  $\alpha$ -tocopherol content, and quantitative capsule rupture test as an *in vitro* dissolution release surrogate), and microbial tests.

The main chemical change observed in the stability studies is (b) (4)

(b) (4)

According to the CMC review, this reaction has been well characterized by the applicant, and the resulting values will comply with the shelf-life acceptance criteria of (b) (4) % for at least 30 months when stored at 25°C.

The CMC review notes that, in general, impurity limits are very low. Regarding chemical substances formed by secondary reactions, (b) (4) is controlled by a specification of NMT (b) (4) ppm ((b) (4)  $\mu$ g/g). As described in the nonclinical section below, the Pharm/Tox review team initially considered the applicant's proposed limit for (b) (4) to be a potential safety issue, recommending an acceptance limit of NMT

(b) (4) ppm. The applicant was notified and, in response, provided justification for (b) (4) ppm, which was accepted by the Pharm/Tox reviewers.

### **Biopharmaceutics**



### **Microbiology**

The Microbial Limits specification for Epanova Capsules was found acceptable by Bryan Riley, PhD, who recommended the submission for approval from the standpoint of product quality microbiology.

### **Facilities Review/Inspection**

On 24 April 2014, the Office of Compliance issued an "Acceptable" overall recommendation for this NDA. There are no pending cGMP inspection issues.

## **4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

Nonclinical data were reviewed by Parvaneh Espandiari, PhD, who recommends approval without further requirements for nonclinical studies.

The applicant submitted nonclinical studies in mice, rats, and dogs; a full panel of genotoxicity studies; two carcinogenicity studies; and a full ICH S5 battery of reproductive toxicology. Nonclinical studies were conducted with oral (gavage) omega-3-carboxylic acids (extracted from Epanova soft-gel capsules) in mice and rats, and with oral Epanova soft-gel

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<sup>2</sup> Meeting minutes dated 23 January 2014.

capsules in dogs. No nonclinical pharmacology studies were conducted, and nonclinical ADME studies were not submitted.

Repeat-dose toxicity studies showed the intended pharmacological effect of Epanova (reductions in total cholesterol and triglycerides). The liver was the potential target organ for toxicity across species based on increased liver enzymes, which were associated with increased liver weight and focal necrosis in some studies. In a 36-week dog study, 2/4 dogs at 1000 mg/kg/day were noted to have 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 MRHD (4 g/day)<sup>3</sup> were 5-fold in the 4-week mouse study (at 4000 mg/kg/day omega-3-carboxylic acids), 2-fold in the 26-week rat study (at 600 mg/kg/day omega-3-carboxylic acids), and 3-fold in the 36-week dog study (at 300 mg/kg/day Epanova capsules).

A full panel of genotoxicity was completed and did not raise safety concerns.

Findings from the reproductive and developmental toxicity studies suggested no treatment effects on reproductive performance, early embryonic development, or maternal or fetal toxicity in rats up to 2000 mg/kg/day (5-fold safety margin to the MRHD of 4 g/day). In pregnant rabbits, there were no maternal effects up to 500 mg/kg/day (~2.4-fold margin to MRHD of 4 g/day). At this dose, however, there were effects on embryo-fetal development: skeletal malformations, ossification effects (variations), and visceral variations. At higher exposure (750 mg/kg/day), there was evidence of maternal toxicity and abortions, as well as fetal skeletal variation. Thus, the NOAEL for embryo-fetal development was established at 100 mg/kg/day (~0.5-fold to MRHD of 4 g/day).

In a pre/post-natal rat study, 9 of 24 F0 animals treated with 2000 mg/kg/day died as a result of difficulties during or shortly after parturition. At F1, there were no effects on growth or development or on their ability to initiate and maintain a pregnancy. However, there was an increased incidence of pup (F2) mortality at 600 and 2000 mg/kg/day. The safety margin to the MRHD (4 g/day) was 1.5-fold (at 600 mg/kg/day) for the F0 generation and 0.25-fold (at 100 mg/kg/day) for the F1 generation.

Two carcinogenicity studies were conducted in rats (2 year) and Tg.rasH2 mice (26 weeks) with oral (gavage) omega-3-carboxylic acids. In the Tg.rasH2 mouse study, no drug-related tumors were observed up to 2000 mg/kg/day (5-fold safety margin to the MRHD of 4 g/day). In the rat study, benign sex cord stromal tumors of the ovaries were reported in female rats treated with 2000 mg/kg/day (5-fold margin to the MRHD of 4 g/day), which was statistically significant for both trend (P=0.0005) and pairwise comparison (P=0.0054), and which exceeded concurrent control and historical controls. Mortality for this study was statistically

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<sup>3</sup> In this section, all safety margins to the MRHD are based on body surface area comparisons.

significant, but cause of death was non-neoplastic, instead being based on microscopic gavage/reflux-related findings in the respiratory tract that exhibited a dose response.

Late in the review cycle, CMC identified (b) (4) as an impurity in the drug substance. The nonclinical review notes that (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. A risk analysis was performed and considered along with the applicant's submitted justification for the proposed specification ((b) (4) ppm) for this impurity. Interestingly, ovarian stromal tumors are part of the tumor profile of (b) (4) and, as noted above, benign sex cord stromal tumors were also observed in the rat carcinogenicity study at (b) (4) mg/kg/day, which would be a human equivalent dose (HED) of (b) (4) g/day for a 60-kg person. (b) (4) was present at (b) (4) ppm (i.e., (b) (4) mg/kg) in the drug lot used in the rat carcinogenicity studies; therefore, the HED of (b) (4) associated with the benign tumors in rat was (b) (4) ng. Setting the specification for (b) (4) at (b) (4) ppm ((b) (4) mg/kg) could lead to the human ingestion of (b) (4) ng/day when taking Epanova 4 g/day (i.e., 0.004 kg/day \* (b) (4) mg/kg \* 10<sup>6</sup> ng/mg = (b) (4) ng/day), (b) (4). The Agency informed the applicant that the (b) (4) specification should be as low as possible because of this concern. The applicant indicated that (b) (4) it was lower than those based on ICH M7 guidelines for genotoxic impurities and (b) (4).

## 5. CLINICAL PHARMACOLOGY

The clinical pharmacology data to support approval of Epanova were reviewed by Suryanarayana Sista, PhD. The Office of Clinical Pharmacology (OCP) recommends approval with the following recommendations: (1) recommended daily dose of 2 g/day, taken as a single 2-gram dose (2 capsules); (2) maximum daily dose should not exceed 4 grams (4 capsules); and 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, at the time of initiating or ending Epanova treatment. OCP requests no post-marketing studies.

Five clinical pharmacology trials were conducted: two phase 1 trials in healthy subjects (including multiple-dose comparison to Lovaza, drug-drug interaction with simvastatin, warfarin, and aspirin), one phase 2 trial in healthy subjects to compare the bioavailability of EPA and DHA from Epanova and Lovaza, and two phase 3 trials from which pharmacokinetic (PK) data were available. In addition, there were five supportive studies: one phase 1 study in healthy subjects to evaluate dose proportionality; one phase 2 study in Crohn's disease to evaluate safety, PK, and pharmacodynamics (PD); and three phase 3 trials in Crohn's disease to evaluate safety and efficacy of Epanova. Last, there were two human

biomaterial studies that provided supporting information on the clinical pharmacology of Epanova.

### Pharmacokinetics

Key PK properties of Epanova are summarized in the following table, excerpted from Dr. Sista's review (p. 8).

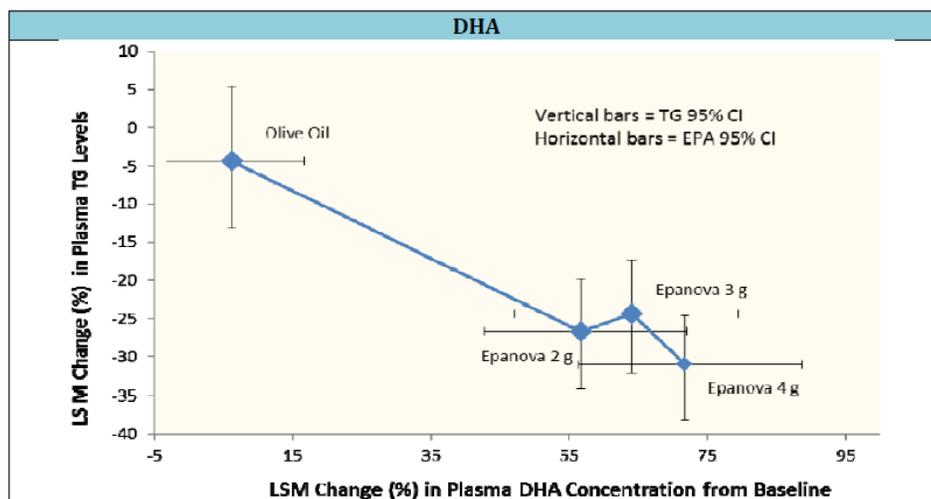
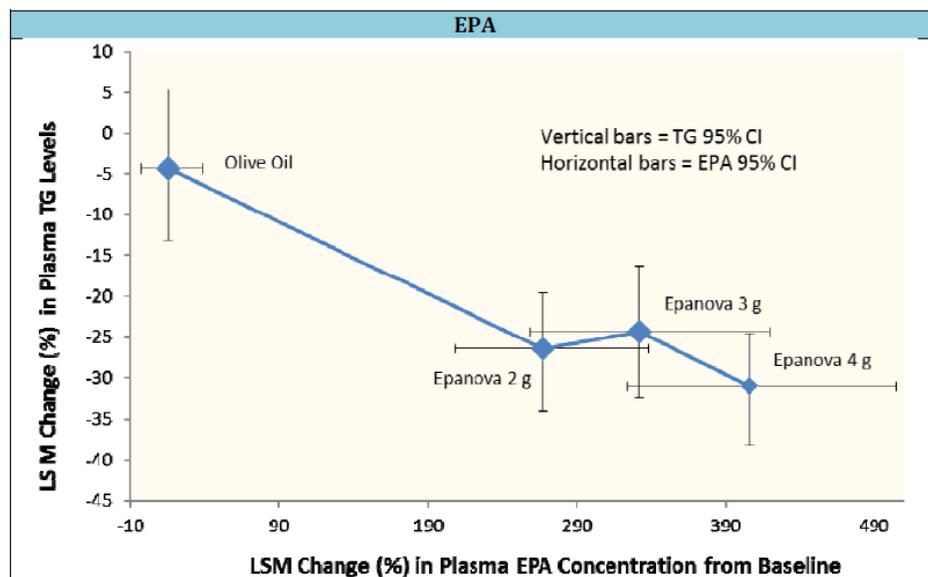
<b>Proposed dose</b>	<ul style="list-style-type: none"><li>• (b) (4) 2 g/day as a single dose;</li><li>• (b) (4) 4 g/day as a single dose</li></ul>
<b>Absorption</b>	<ul style="list-style-type: none"><li>• Linear pharmacokinetics between 2 g and 8 g doses</li><li>• Median T<sub>max</sub> - EPA: ~ 4.5 - 5.5 h; DHA: 4.7 - 5.3 hrs</li><li>• t<sub>1/2</sub> - EPA: 4.7 - 10.8 h; DHA: ~7 h</li><li>• Mean EPA and DHA trough levels similar at 16 and 52 weeks of daily dosing of 4 g Epanova</li><li>• approximate 2-fold accumulation of EPA during continued dosing</li><li>• Steady-state concentrations achieved within 2 weeks of 4 g once-daily dosing</li></ul>
<b>Distribution</b>	<ul style="list-style-type: none"><li>• Following a single 4 g dose of EPANOVA under fasted conditions, the vast majority of EPA and DHA in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, with the free unesterified fatty acid representing approximately 0.8% and 1.1% of the total measured amount for EPA and DHA, respectively.</li></ul>
<b>Metabolism and Elimination</b>	<ul style="list-style-type: none"><li>• Similar to fatty acids derived from dietary sources, EPA and DHA from Epanova are mainly oxidized in the liver. Following repeat dosing under low-fat meal conditions, the total plasma clearance (CL/F) and half-life of baseline-adjusted EPA from Epanova at steady-state are 548 mL/hr and 36 hours, respectively, while that of DHA are 518 mL/hr and approximately 46 hours, respectively. Epanova does not undergo renal excretion.</li></ul>

### Dose-Response for Efficacy

Three doses of Epanova were studied in the pivotal phase 3 trial for severe hypertriglyceridemia: 2 g, 3 g, and 4 g/day. Of the fatty acid components, only EPA and DHA exposures were quantitated in clinical trials. Dr. Sista concluded that no clear dose-response relationship between TG lowering and EPA or DHA exposure was observed across these doses, as shown in the figures below, excerpted from his review (p. 9).<sup>4</sup>

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<sup>4</sup> Original source: *Module 2.7.2 Summary of Clinical Pharmacology Studies*, Figure 2.7.2-22, page 47.



### Intrinsic Factors

Age, gender, race, and body weight were not found to have clinically relevant effects on the pharmacokinetics of EPA or DHA.<sup>5</sup> Effects of renal and hepatic impairment were not studied.

### Food Effect

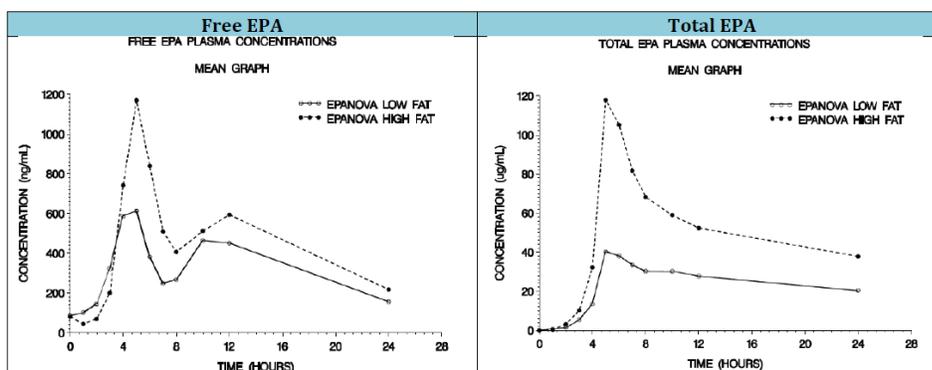
OM-EPA-001 evaluated the effect of fasting/low-fat and high-fat meals on the bioavailability of EPA and DHA after a single dose of Epanova. This was a randomized, open-label, 4-way crossover study, with 4 single-dose treatment periods and a minimum 7-day washout between each treatment. Each treatment period consisted of an in-clinic stay for 12 hours and

<sup>5</sup> Only data from studies OM-EPA-001 (healthy volunteers; food-effect study) and OM-EPA-006 (healthy volunteers; warfarin DDI and comparison of systemic exposure of Epanova and Lovaza following multiple-dose administration) could be pooled for this analysis, since both used an LC/MS/MS assay for free EPA, free DHA, total EPA, and total DHA.

a 24-hour follow-up visit. Subjects were randomly assigned (1:1) to the sequence ELEL or LELE (E=Epanova; L=Lovaza). Meals assigned to each period were fixed: low-fat (~5% of total meal kcal) for periods 1 and 2, and high-fat (30% of total meal kcal) for periods 3 and 4.

For the low-fat periods, subjects fasted for 12 hours, ingested Epanova 4 g (fasting), had a no-fat lunch after the 4-hr blood draw, and had a low-fat dinner after the 12-hr blood draw before leaving the clinic. For the high-fat periods, subjects fasted for 12 hours, ate a high-fat breakfast immediately following the -0.5-hr blood draw, ingested Epanova 4 g, and had a high-fat lunch and dinner after the 4-hr and 12-hr blood draws, respectively.

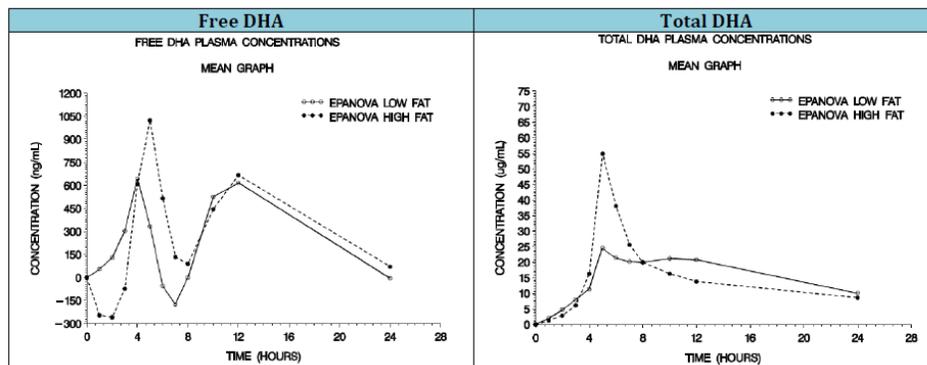
Regarding EPA, the relative bioavailability of total EPA was lower when Epanova was administered with a fasting/no-fat/low-fat diet than with a high-fat diet (AUC<sub>0-t</sub> ratio 41.9% and 55.6% adjusted and unadjusted for baseline, respectively). Similarly, the relative bioavailability of free EPA was lower when Epanova was administered with a fasting/no-fat/low-fat diet than with a high-fat diet (AUC<sub>0-t</sub> ratio 56.6% and 68.7% adjusted and unadjusted for baseline, respectively). The figures below are excerpted from Dr. Sista's review (p. 60).<sup>6</sup>



Regarding DHA, the relative bioavailability of total DHA was similar whether Epanova was administered with a fasting/no-fat/low-fat diet or a high-fat diet (AUC<sub>0-t</sub> ratio 106.4% and 94.3% adjusted and unadjusted for baseline, respectively). The relative bioavailability of free DHA was also similar regardless of diet (AUC<sub>0-t</sub> ratio 70.2% and 100.9% adjusted and unadjusted for baseline, respectively). The figures below are excerpted from Dr. Sista's review (p. 61).<sup>7</sup>

<sup>6</sup> Original source: Study OM-EPA-001, Figures 14.2.2.3.3 and 14.2.5.3.3.

<sup>7</sup> Original source: Study OM-EPA-001, Figures 14.2.3.3.3 and 14.2.6.3.3.



Dr. Sista concludes that there appears to be a food effect with Epanova. However, given that patients with severe hypertriglyceridemia are instructed to avoid high-fat meals and that patients were instructed to dose Epanova without regard to meals in the pivotal phase 3 trial, it seems most appropriate not to encourage taking Epanova with high-fat meals in labeling.

### Drug-Drug Interactions

The potential for Epanova to inhibit cytochrome P450s<sup>8</sup> was assessed *in vitro* in a pooled microsomal preparation in the presence of 10 µM Epanova (chosen to represent the physiological levels of free fatty acids in the liver of healthy individuals) and 200 µM Epanova (chosen to represent levels 100-fold greater than the expected physiological range, also being the apparent maximum solubility of Epanova in the test system matrix). Based on the results of this study, further examination of the *in vitro* inhibition potential of Epanova for 2B6, 2C8, and 2C9 was conducted over concentrations of 0.1, 1, and 10 µM Epanova. The results demonstrated that Epanova exerts no inhibition potential on CYP2B6, CYP2C8, and CYP2C9 in the tested concentration range.

### Simvastatin

OM-EPA-007 was a drug-drug interaction (DDI) study that assessed the effect of multiple daily doses of Epanova 4 g on the PK of multiple 40-mg doses of simvastatin. Low-dose aspirin (81 mg daily) was also administered with simvastatin. Daily administration of simvastatin 40 mg with Epanova 4 g did not affect the extent (AUC) or rate ( $C_{max}$ ) of exposure to simvastatin or its major active metabolite,  $\beta$ -hydroxy simvastatin, at steady state.

### Aspirin

Although the main objective of OM-EPA-007 was to evaluate for a DDI between Epanova and simvastatin, the sponsor also sought to determine whether there is a pharmacodynamic DDI between Epanova and aspirin using the VerifyNow-Aspirin assay. This is a turbidimetric-based optical detection system that measures platelet aggregation as an increase in light transmittance, in which aggregation is induced by fibrinogen-coated microparticles. This assay did not suggest a DDI between Epanova and aspirin, but this assay would be

<sup>8</sup> CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, and 4A11.

insensitive to detect Epanova-induced changes in thromboxane production, which would be more relevant to the hypothesis underlying how a fish oil-derived product may modulate aspirin's pharmacodynamic effect.<sup>9</sup> [REDACTED] (b) (4)

### Warfarin

OM-EPA-006 was a DDI study that assessed the effect of multiple daily doses of Epanova 4 g on the PK/PD of a single 25-mg dose of warfarin. In addition to measuring the PK of R- and S-warfarin, PD endpoints included the maximum INR during the 168 hours post-dose and the INR AUC<sub>0-168h</sub>. This study demonstrated that Epanova 4 g/day does not significantly affect the single-dose AUC or C<sub>max</sub> of R- or S-warfarin, or the INR profile following a single dose of warfarin 25 mg. Dr. Sista notes, however, that the interaction potential of steady-state Epanova on steady-state administration of warfarin is unknown; therefore, monitoring of INR is recommended as described previously.

### QTc Assessment

A thorough QT (TQT) waiver was granted for Epanova.<sup>10</sup> Instead, the sponsor proposed to collect 12-lead ECGs at baseline (Visit 3/Week -1) and at steady state (Visit 8/Week 12 or early termination). ECGs were originally read by the investigator at each clinical site, and paper ECGs were sent retrospectively to a central laboratory for a blinded high-resolution reading by a cardiologist masked to study treatment.

In a consult review signed 16 December 2013, the QT-IRT stated that they reviewed the applicant's submission and concluded that ECG data from OM-EPA-003 (EVOLVE) do not show proarrhythmic liability for Epanova. Furthermore, they reiterated comments from a previous consultation dated 19 July 2012 that mean changes from baseline for placebo-corrected QTcF, PR, and QRS duration were not clinically relevant for any dose group (2, 3, or 4 g/day). No subject had a QTcF >500 ms or a post-baseline increase >60 ms. No subject had an increased incidence in morphological ECG changes compared with placebo. The mean change from baseline for placebo-corrected heart rate was not clinically relevant.

## 6. CLINICAL/STATISTICAL- EFFICACY

One pivotal phase 3 clinical trial (OM-EPA-003, or EVOLVE) was conducted to support the efficacy of Epanova in reducing TG levels in patients with severe hypertriglyceridemia. Supportive efficacy/safety data for patients with hypertriglyceridemia were provided from a second phase 3 clinical trial (OM-EPA-004, or ESPRIT), which enrolled statin-treated patients

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<sup>9</sup> Omega-3 fatty acids have been described to alter platelet eicosanoid formation, shifting TxA<sub>2</sub> (derived from arachidonic acid) to the less-active TxA<sub>3</sub> (Leaf A and Weber PC. Cardiovascular effects of n-3 fatty acids. *N Engl J Med* 1988; 318:549-557).

<sup>10</sup> QT-IRT consult reviews signed 19 July 2012 and 27 September 2012, IND 107616.

with TG levels between 200 and 500 mg/dL. Because severe hypertriglyceridemia is the only population under consideration for a treatment indication in this NDA, I will limit my discussion of efficacy to the EVOLVE trial. Furthermore, I will place additional emphasis on dose-response, as it relates to Dosing and Administration recommendations, since this was a major source of discussion among the review team for this application.

Prior to NDA submission, the Division agreed to accept a single pivotal phase 3 trial for review to support an indication for severe hypertriglyceridemia.<sup>11</sup> The EVOLVE study design, described below, was agreed upon under a Special Protocol Assessment (agreement letter dated 22 Oct 2010).

## **EVOLVE**

The EVOLVE trial was a 12-week, multinational, randomized, double-blind, placebo (olive oil)-controlled trial that aimed to evaluate the efficacy and safety of Epanova in subjects with severe hypertriglyceridemia (TG  $\geq$ 500 and  $<$ 2000 mg/dL). The trial was conducted at 74 centers in 7 countries between April 2011 and February 2012.<sup>12</sup>

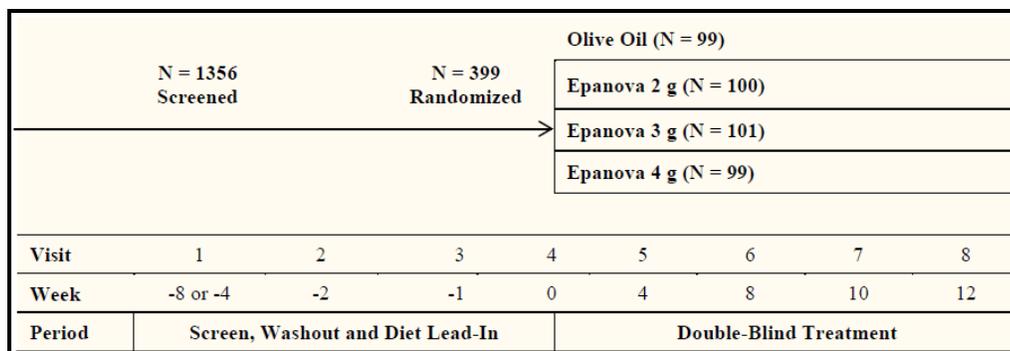
As shown in the flow diagram below from Dr. Iffat Chowdhury's clinical efficacy review (p. 38), patients entered a 4- to 8-week washout/diet (NCEP TLC) lead-in period.<sup>13</sup> Those with a fasting TG level  $\geq$ 500 and  $<$ 2000 mg/dL (average of 2-3 measurements) were randomly assigned with equal allocation to one of four groups for a 12-week treatment duration: placebo (olive oil; n=99), Epanova 2 g/day (n=100), Epanova 3 g/day (n=101), or Epanova 4 g/day (n=99). Randomization was stratified according to use of permitted lipid-altering drugs (yes/no). Because Epanova capsules are only available in a 1-gram dosage form, subjects in the 2 g/day and 3 g/day group also received olive oil capsules such that each subject took 4 capsules once daily to maintain blinding. Patients took study drug without regard to meals.

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<sup>11</sup> See IND 107616 "Special Protocol Assessment – No Agreement" letter (27 Aug 2010), "Special Protocol – Agreement" letter (22 Oct 2010), and 14 Nov 2012 Pre-NDA Meeting Minutes (18 Dec 2012).

<sup>12</sup> Countries, in decreasing order of contribution to the randomized population, included Hungary (32%; n=127), the United States (28%; n=110), Russia (15%; n=60), Ukraine (9%; n=34), Denmark (7%; n=28), the Netherlands (6%; n=22), and India (5%; n=28). [Source: Demographics dataset, *dm.xpf*]

<sup>13</sup> Subjects previously on omega-3 drugs/supplements needed to washout for 8 weeks. Subjects who required adjustment or addition of a permitted statin, ezetimibe, or statin/ezetimibe combination, needed to stabilize for 8 weeks before randomization (6 weeks prior to first TG eligibility measurement). All other subjects, including those who discontinued bile acid sequestrants, fibrates, niacin, or other lipid-altering supplements needed to washout for 4 weeks prior to randomization.



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

The primary efficacy endpoint was the percent change in fasting TG from baseline (average of Weeks -2, -1, and 0) to the end of treatment (average of Weeks 10 and 12). Secondary efficacy endpoints included the percent change in fasting non-HDL-C and HDL-C from baseline to the end of treatment. There were multiple tertiary endpoints, including other lipid/lipoprotein parameters, plasma levels of fatty acids, and inflammatory markers.<sup>14</sup> Efficacy analyses were performed on the modified intent-to-treat (mITT) population, which comprised all randomized subjects who received at least one dose of investigational product and had at least one post-randomization efficacy assessment.<sup>15</sup>

Regarding demographic and baseline characteristics, the mean age of the study population was 52 years, 77% were male, 92% white/Caucasian, and 6% Asian. Overall, 37% had diabetes and 35% were taking a statin (with or without ezetimibe). Mean BMI was 31 kg/m<sup>2</sup>. Although baseline characteristics appeared reasonably similar across the four groups of this 399-subject trial, the statistical reviewer, Ms. Cynthia Liu, noted that there was an imbalance with regard to the proportion of subjects ≥65 years old (11%, 8%, 4%, and 16% for the placebo and Epanova 2 g, 3 g, and 4 g groups, respectively). Given the relatively few number of patients older than 65 years in this trial (39 total in the mITT population), I do not believe that this imbalance would be expected to have a meaningful impact on the interpretation of the trial's results.

As shown in Table 12 (p. 45) of Dr. Chowdhury's review, in the mITT population overall, the median baseline TG was 694 mg/dL. Across groups, the median baseline TG values were 682 (placebo), 717 (Epanova 2 g), 728 (Epanova 3 g), and 655 (Epanova 4g) mg/dL. Median baseline values for other fasting lipid parameters included non-HDL-C 217 mg/dL, HDL-C 28 mg/dL, VLDL-C 124 mg/dL, direct LDL-C 81 mg/dL, and TC 246 mg/dL for the mITT population overall.

<sup>14</sup> Tertiary efficacy endpoints included serum TC, LDL-C, TC/HDL ratio, VLDL-C, apoA-I, apoB, apoC-III, RLP-C, lipoprotein particle characteristics, HgbA1c, Lp-PLA<sub>2</sub>, hs-CRP, and plasma EPA, DHA, and AA. Visits used to define "baseline" and "endpoint" were not the same as the primary and secondary efficacy endpoints given the collection schedule for these exploratory parameters.

<sup>15</sup> For the primary outcome (TG), the numbers of ITT patients excluded from the mITT population were 1, 1, 4, and 0 for the placebo and Epanova 2 g, 3 g, and 4 g groups, respectively.

Primary, secondary, and tertiary continuous efficacy endpoints were analyzed using an ANCOVA model with treatment and use of lipid-altering drugs (yes/no) as factors and baseline as a covariate. Data were ranked prior to inferential testing because of non-normality, as specified in the statistical analysis plan (SAP). Furthermore, data were log-transformed to obtain least-squares mean changes from baseline.<sup>16</sup> Type I error was controlled for multiple comparisons for the primary and secondary endpoints. LOCF was the primary method for missing data handling, with sensitivity analyses using a multiple imputation method and a mixed model repeated measures (MMRM) approach.

Approximately 91% of study subjects completed the 12-week trial, ranging from 86% in the Epanova 3 g/day group to 95% in the placebo group. In the Epanova groups, 17 (57%) of the 30 premature trial discontinuations were the result of adverse events (primarily gastrointestinal); none of the 5 premature discontinuations in the placebo group were the result of adverse events. The mITT population comprised >98% of the randomized population.

**Primary Efficacy Variable: TG**

General Note: In the descriptive text that follows, I will present the treatment effects as described by the applicant and confirmed by the statistical reviewer. However, given the skewed distributions of the data, the review team believes it is most appropriate to describe within-group changes in lipid parameters from baseline to endpoint as median percent change and the between-group changes (Epanova dose group vs. placebo) using Hodges-Lehmann estimates of the treatment difference. Summary tables from the statistical review with these data are provided at the end of this discussion on efficacy.

Ms. Liu verified the sponsor's results. All Epanova dose groups showed a statistically significantly greater mean percent decrease in TG from baseline to end of treatment, compared with the placebo (olive oil) group.<sup>17</sup> The placebo-adjusted mean treatment differences were -21.7%, -21.2%, and -26.6% for the Epanova 2 g, 3 g, and 4 g/day groups, respectively, using the sponsor's approach of log-transforming the data. The P values obtained from rank-transformed data using an ANCOVA model<sup>18</sup> were 0.005, 0.007, and <0.001 for the three Epanova doses compared to placebo, respectively, and robust to

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<sup>16</sup> In the EVOLVE SAP (v4.0, 21 Feb 2012), there is no mention of log transformation of data. The statistical review team has noted during labeling discussions that there are different methods of log-transforming the data, which result in different estimates of the treatment effect. Thus, considering the skewed distributions, they have recommended that Hodges-Lehmann estimates of the median treatment difference would be most appropriate for labeling, which is the approach used in the Vascepa and Omtryg labels. The level of statistical significance, however, would be reported using the P values obtained from the pre-specified analyses described in the SAP (ANCOVA model using rank-transformed data).

<sup>17</sup> In the sponsor's EVOLVE protocol, they state "Regarding the choice of placebo control, olive oil is a standard for placebo in omega-3 trials because it does not affect triglyceride levels or arachidonic acid production," citing Harris WS. n-3 fatty acids and serum lipoproteins: human studies. *Am J Clin Nutr* 1997; 65:1645S-1654S.

<sup>18</sup> ANCOVA model included terms for treatment, baseline value as a covariate, and the stratification factor (user of permitted lipid-altering drugs: yes/no).

sensitivity analyses to assess the impact of missing data.<sup>19</sup> The data were highly skewed, especially in the placebo group where the mean percent change was +9.5% and the median percent change was -10.4%. The primary results, as summarized by the sponsor and reproduced in the statistical review (p. 13), are shown below.

Table 4 – Efficacy Results for TG (mg/dL) (extracted from sponsor’s table)

Triglycerides	Olive Oil (N=99)	Epanova		
		2 g (N=100)	3 g (N=101)	4 g (N=99)
<b>MITT Population</b>				
Baseline (mg/dL) [1]				
N	98	99	97	99
Mean (SD)	788.5 (305.11)	790.1 (269.01)	820.4 (353.15)	783.6 (335.21)
Median	682.3	717.0	728.0	655.0
Min, Max	417.7, 2006.5	415.3, 1577.8	438.7, 2157.7	435.3, 2094.7
% Change from Baseline [2]				
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
Min, Max	-64.2, 424.7	-88.5, 101.1	-84.2, 520.1	-78.4, 105.0
LSM [3]	-4.26	-25.94	-25.46	-30.86
95% CI	(-13.07, 5.44)	(-32.84, -18.33)	(-32.44, -17.75)	(-37.32, -23.74)
LSM Difference from Olive Oil		-21.68	-21.19	-26.60
95% CI Bonferroni-corrected		(-40.70, -2.89)	(-40.32, -2.29)	(-45.12, -8.38)
P-value [4]		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.

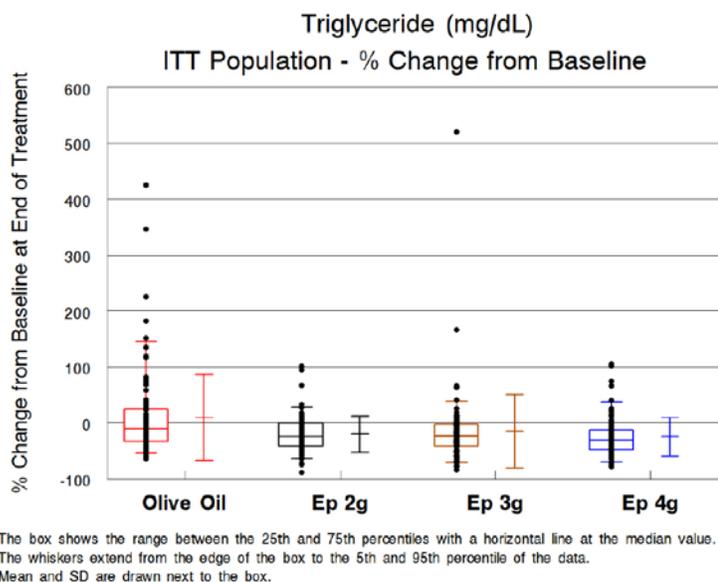
[4] P-value from treatment effect in ANCOVA model that included terms for treatment, baseline value as a covariate, and a stratification factor for users and non-users of permitted lipid-altering drugs. P-values are adjusted using Dunnett’s procedure for multiple comparisons of each Epanova vs. olive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

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

Source: Extracted from Table 11.4.1 in sponsor’s clinical study report

Ms. Liu also performed a non-parametric test on the percent change data and presented the Hodges-Lehmann median estimates with 95% CIs: -15.5% (-25.5%, -5.7%), -15.4% (-26.0%, -5.2%), and -20.8% (-31.2%, -11.1%) for the Epanova 2 g, 3 g, and 4 g doses, respectively, relative to olive oil. The distributions of percent change from baseline to end of treatment are depicted in the following figure, excerpted from the statistical review (p. 14).

<sup>19</sup> According to the statistical review, the missing data rates on the TG endpoint were 5%, 6%, 13%, and 7% in the placebo and Epanova 2 g, 3 g, and 4 g dose groups, respectively.



Although it is straightforward to conclude that Epanova treatment, at 2 grams to 4 grams daily, produces a statistically significant reduction in TG compared with olive oil, the review team found it more challenging to use the available data to generate recommendations for Dosing and Administration. Dr. Chowdhury notes in her review (pp. 52-53), “Although all three doses of Epanova decreased TG, the result for the 3 g dose was numerically similar to the 2 g dose. . . . Therefore there was no benefit of 3 g over 2 g for TG reduction. Patients in the 4 g 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.”

Ms. Liu made similar observations. She states in her review (p. 13), “Although determination of dose-response was not the study objective, I performed the Jonckheere-Terpstra non-parametric test as an exploratory analyses to assess the association between the TG lowering and Epanova doses. The test showed that there was no statistically significant correlation indicating that greater reductions in TG were associated with higher Epanova doses (two-sided  $p=0.20$ ).” She later concludes (p. 33), “Although the 3 doses of Epanova were all effective in reducing TG and non-HDL-C, the dose-response was modest. In fact, the observed treatment effects from the 3 g dose on TG and non-HDL-C lowering were numerically slightly smaller than that from the 2 g dose. Therefore, whether to approve higher doses or not will need to take safety into consideration.”

On 05 March 2014, the Division sent an information request to the applicant noting, in part, that despite large increases in plasma EPA from the 2 g to 4 g dose, the difference in TG lowering was modest. The applicant was offered the opportunity to expand on their justification for approving the 2 g and 4 g doses, as they had proposed in the Dosage and Administration section of labeling. The applicant responded in a 21 March 2014 amendment, and Dr. Chowdhury summarized their justification in her review (pp. 81-84). To briefly summarize, the applicant offered the following:

- "...there was a clear dose-dependence in the number of subjects who had met the NCEP ATP III threshold of having TG <500 mg/dL at the end of treatment. After 12 weeks of treatment with 2 g and 4 g/day EPANOVA, 38.9% and 51.6% of subjects, respectively, had TG <500 mg/dL."
- "While the 2 g/day EPANOVA regimen had a potent TG lowering efficacy (-26%), there was a clinically meaningful incremental benefit with the 4 g/day dosage (-31%). 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."
- Regarding benefit/risk, the applicant emphasized the observed incremental TG-lowering between 2 g and 4 g, then noting, "The safety analyses in EVOLVE demonstrated a favorable safety profile for the 2 and 4 g/day dosing with EPANOVA.... [T]here 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."
- In an *ad hoc* analysis, "...it was shown that a dose-dependent increase in the number of subjects achieving greater TG reductions in the 4 g versus the 2 g EPANOVA regimen became apparent for >30% and >40% TG reductions. And, at the lowest category of TG reductions (10% or less), both the olive oil and the 2 g dose groups had the largest number of subjects. Therefore, the 4 g EPANOVA dose was apparently more effective than the 2 g dose across the range of baseline TG levels."
- Last, the applicant conducted a second *ad hoc* analysis in a subgroup of subjects with baseline TG >885 mg/dL. "Although the sample sizes in the three groups were relatively small (N=25 to 31), there was a clear dose-response between the 2 g and 4 g regimens. The median percent changes from baseline for the 2 g and 4 g per day regimens differed by almost 12%..."

Dr. Chowdhury considered the applicant's justification to support both the 2 g and 4 g doses and stated, "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" (p. 83). She notes, however, that the effect of the incremental TG reduction on the clinical outcome that one hopes to be affecting with TG-lowering therapy in this population (i.e., pancreatitis) is unknown.

Regarding the sponsor's justification regarding the proportion of patients who achieve TG <500 mg/dL (sponsor's definition of "responder"), Ms. Liu confirmed their analysis and also conducted a sensitivity analysis in which subjects with missing values at Week 12 were considered "non-responders." The patterns were similar, as shown in the following table, excerpted from her review (p. 14).

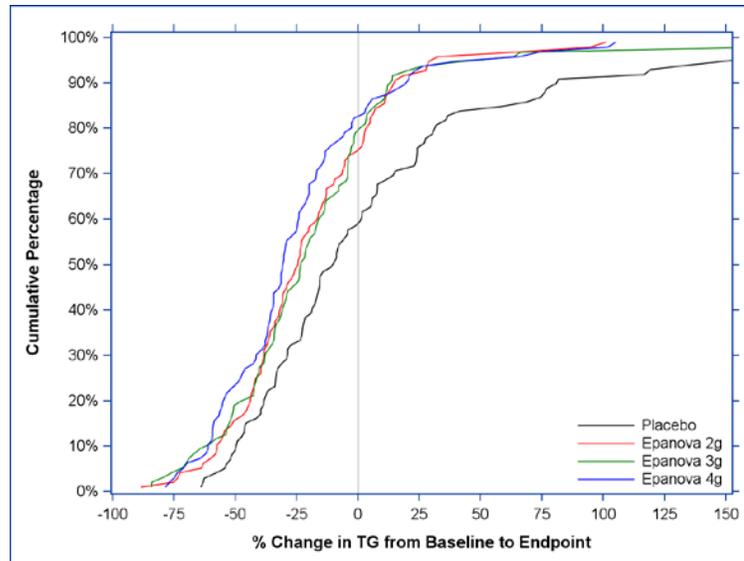
Table 5 – Responder Rate for TG < 500 mg/dL at Week 12

ITT Population	Olive Oil	Epanova 2 g	Epanova 3 g	Epanova 4 g
Sponsor's	36/98 (37%)	37/95 (39%)	42/94 (45%)	49/95 (52%)
Reviewer's <sup>1</sup>	36/99 (36%)	37/100 (37%)	42/101 (42%)	49/99 (49%)

<sup>1</sup> Subjects with missing data at Week 12 were treated as non-responders.

Although I have included these descriptive results here for completeness, I do not find such "responder" data to provide much additional useful information. To call these patients "responders" requires one to accept that 37% of olive oil-treated patients "responded" to olive oil 4 g/day, which would be rather surprising given that the sponsor chose olive oil as a placebo because of its minimal effect on TG; it is more likely that many of these patients achieved TG <500 mg/dL for reasons other than the administered treatment. Thus, the proportions in this table do not reflect how many patients achieved TG <500 mg/dL because of Epanova. Although between-group differences could be used to infer a treatment effect, this is unnecessary given the results described previously based on the changes detected based on measures of central tendency. As mentioned in Dr. Chowdhury's review (p. 8), an exploratory analysis for trend across the Epanova 2 g, 3 g, and 4 g doses did not exclude the possibility that the observed differences in proportions could have occurred by chance (p=0.08).

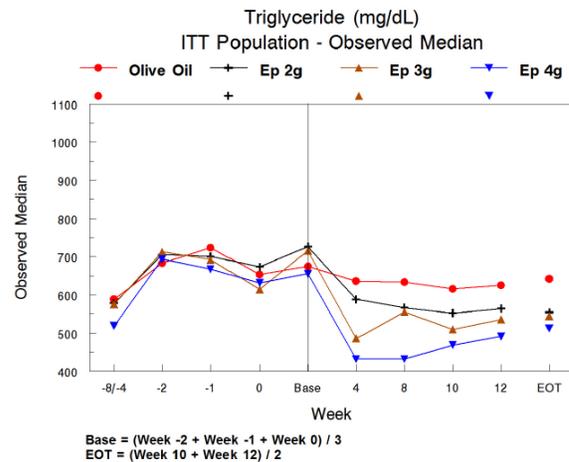
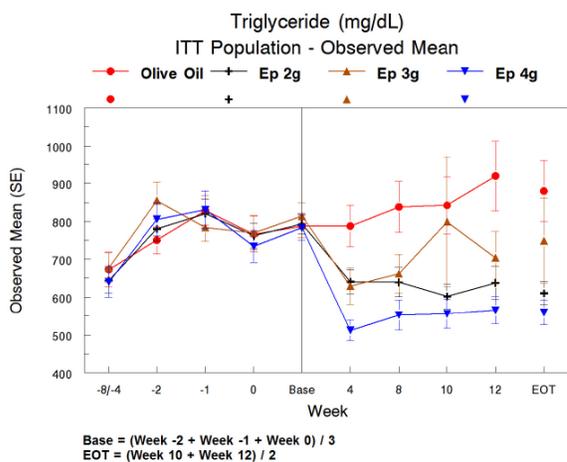
However, given the safety profile of Epanova (discussed in Section 7 of this memo), I do agree with Dr. Chowdhury that it is reasonable to provide dosing recommendations that include both the 2 g and 4 g daily doses. The lack of statistical significance (or overlapping 95% CIs) between doses does not bother me, *per se*, as this trial was not powered to detect such small differences, although I do agree with Dr. Chowdhury that the fact that the true differences between doses are likely quite small does call into question whether the doses would be expected to have any meaningful difference in clinical outcomes. The sponsor's justification that I find the most compelling is the observation that a greater proportion of patients in the Epanova 4 g group had larger reductions (e.g., >30%, >40%) than in the Epanova 2 g group. Rather than simply looking at arbitrary cutpoints as the applicant did, I plotted the cumulative distribution function for percent change in TG for all 4 groups, below.



Source: Clinical Team Leader’s analysis from EVOLVE *adef.xpt* dataset  
 Note: x-axis truncated at 150% for clarity.

In this figure, a shift to the left from the placebo (black) curve indicates a greater TG-lowering effect than placebo. Although one cannot discern a difference between 2 g/day and 3 g/day, it does appear that a greater proportion of patients in the 4 g/day group achieve a given TG reduction (or greater) than in the 2 g/day group.

Last, both Dr. Chowdhury and Ms. Liu point out that the longitudinal TG profile suggests the possibility of a waning effect in the Epanova 4 g/day group (reproduced in the figures below, excerpted from the statistical review, p. 14). Although the statistical review states that “[e]valuation of data after Week 12 may be important since the long-term treatment effect of Epanova on these parameters remains to be seen,” (p. 33), neither reviewer comments that this observation should preclude approval of Epanova 4 g/day. I agree that although it would be ideal to have controlled data for a longer period of time than 12 weeks to obtain a better estimate of the long-term durability of the drug’s effect, the observed longitudinal profile is not compelling enough to preclude approval of the Epanova 4 g/day dosage for severe hypertriglyceridemia.



Regarding secondary efficacy variables, all Epanova groups showed a statistically significantly greater mean percent decrease in non-HDL-C from baseline compared with the placebo group. The placebo-adjusted differences were -10.1%, -9.4%, and -12.2% for the Epanova 2 g, 3 g, and 4 g/day groups, respectively, using the sponsor's approach of log-transforming the data. The P values obtained from rank-transformed data using an ANCOVA model were 0.017, 0.019, and 0.001 for the three Epanova doses compared to placebo, respectively, and robust to sensitivity analyses. For HDL-C, all Epanova groups showed a numerically greater mean percent increase from baseline compared with the placebo group, but these differences were not statistically significant. The placebo-adjusted differences were +5.4%, +1.9%, and +3.8% for the Epanova 2 g, 3 g, and 4 g/day groups compared to placebo, respectively, with P values of 0.076, 0.091, and 0.091.

Regarding tertiary lipid variables, the placebo-adjusted mean changes in VLDL-C were -18.0% (p=0.007), -17.9% (p=0.006), and -24.5% (p <0.001) for the Epanova 2 g, 3 g, and 4 g/day groups, respectively; the placebo-adjusted mean changes in TC were -8.6% (p=0.037), -8.0% (p=0.083), and -10.6% (p=0.003); and the placebo-adjusted mean changes in TC/HDL-C were -11.7% (p=0.024), -8.5% (p=0.049), and -13.0% (p=0.002) for the three Epanova doses, respectively.

Fish oil-derived mixtures that contain both DHA and EPA have been shown to increase LDL-C, and Epanova is not an exception. As Dr. Chowdhury shows in her review, the placebo-adjusted mean changes in LDL-C from baseline to were +16.2% (p=0.003), +11.3% (p=0.072), and +16.4% (p<0.001) for Epanova 2 g, 3 g, and 4 g/day, respectively. Dr. Chowdhury comments, "The absolute atherogenic potential of the increase in LDL-C seen with Epanova treatment in patients with severe hypertriglyceridemia is unknown" (p. 59). She also notes that although there is an increase in LDL-C, there is an overall reduction in non-HDL-C, which is generally thought to reflect the total "atherogenic" cholesterol. Despite the reduction in non-HDL-C, however, I note that we do not have evidence that Epanova reduces ApoB, as one might suspect. Instead, the placebo-adjusted mean changes in ApoB from baseline were +3.0%, +1.4%, and +2.9% for the three Epanova doses (all P >0.3). Ultimately, I believe it is reasonable to address the potential increase in LDL-C in labeling (b) (4)

[REDACTED]

In their reviews, Dr. Chowdhury and Ms. Liu describe treatment effects for TG across multiple subgroups defined by age (<65, ≥65 years), sex, race (white, non-white), country (USA, non-USA), baseline TG (<750, ≥750 mg/dL), and statin with or without ezetimibe use (yes/no). Ms. Liu notes that there were no significant interactions of treatment-by-subgroup observed (all P >0.10). Although one could generate hypotheses from some of the results obtained (based on the point estimates alone), (b) (4)

[REDACTED]

The following two tables, excerpted from the statistical review (pp. 30-31), summarize the within-group changes for the lipid parameters described above and the between-group comparisons to placebo.

Table 18 – Summary of Efficacy Results for Each Study Group

MITT		Olive Oil	Epanova 2 g	Epanova 3 g	Epanova 4 g
TG	Median Baseline (mg/dL)	682.3	717.0	728.0	655.0
	Median % Change	-10.4	-24.5	-23.4	-30.7
	LSM % Change	-4.3	-25.9	-25.5	-30.9
Non-HDL-C	Median Baseline (mg/dL)	214.5	205.3	215.3	225.0
	Median % Change	-0.9	-7.7	-3.6	-7.7
	LSM % Change	2.5	-7.6	-6.9	-9.6
HDL-C	Median Baseline (mg/dL)	28.7	27.3	28.0	28.7
	Median % Change	2.2	7.0	6.9	5.0
	LSM % Change	1.9	7.3	3.8	5.8
LDL-C	Median Baseline (mg/dL)	78.2	77.3	81.0	90.3
	Median % Change	9.8	21.4	16.6	26.2
	LSM % Change	3.0	19.2	14.2	19.3
TC	Median Baseline (mg/dL)	245.5	240.7	243.7	254.3
	Median % Change	-0.3	-6.4	-2.9	-6.2
	LSM % Change	3.2	-5.4	-4.8	-7.5
VLDL-C	Median Baseline (mg/dL)	124.5	123.3	124.0	126.0
	Median % Change	-11.3	-24.7	-21.6	-34.7
	LSM % Change	-8.5	-26.5	-26.4	-33.0
N for baseline: 98, 99, 97, and 99 for olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. N for % Change: 98, 95, 94, and 95 for olive oil, Epanova 2 g, 3 g, and 4 g dose groups, respectively. LSM % change from baseline was obtained from an ANCOVA model using natural-log-transformed data. Source: Summarized from Table 11.4.1 – Table 11.4.4 in sponsor’s clinical study report.					

Table 19 – Summary of Efficacy Results for Between-Group Comparison

MITT	Treatment Difference	Ep 2 g vs. Olive Oil	Ep 3 g vs. Olive Oil	Ep 4 g vs. Olive Oil
TG	LSM difference	-21.7 **	-21.2 **	-26.6 ***
	95% CI Bonferroni-corrected	(-40.7, -2.9)	(-40.3, -2.3)	(-45.1, -8.4)
	Hodges-Lehmann median	-15.5	-15.4	-20.8
	95% CI, unadjusted	(-25.5, -5.7)	(-26.0, -5.2)	(-31.2, -11.1)
Non-HDL-C	LSM difference	-10.1 *	-9.4 *	-12.2 **
	95% CI Bonferroni-corrected	(-21.0, 0.7)	(-20.3, 1.5)	(-22.9, -1.4)
	Hodges-Lehmann median	-7.2	-6.5	-10.3
	95% CI, unadjusted	(-12.6, -2.1)	(-12.7, -1.0)	(-16.1, -4.7)
HDL-C	LSM difference	5.4 NS	1.9 NS	3.8 NS
	95% CI Bonferroni-corrected	(-4.0, 14.9)	(-7.4, 11.1)	(-5.5, 13.2)
	Hodges-Lehmann median	5.1	4.4	3.6
	95% CI, unadjusted	(0.4, 10.3)	(-0.2, 8.6)	(-0.6, 7.8)
LDL-C	LSM difference	16.2	11.2	16.3
	Hodges-Lehmann median	13.1	8.8	15.3
TC	LSM difference	-8.6	-8.0	-10.6
	Hodges-Lehmann median	-5.8	-5.2	-8.7
VLDL-C	LSM difference	-18.0	-17.9	-24.5
	Hodges-Lehmann median	-14.1	-14.3	-20.8
LSM difference was obtained from an ANCOVA model using natural-log-transformed data. * for p < 0.05; ** for p < 0.01; *** for p < 0.001; NS for p not significant at 0.05 level No statistical inferential testing was performed for LDL-C, TC, and VLDL-C since they were tertiary endpoints. Source: Summarized from Table 11.4.1 – Table 11.4.4 in sponsor’s clinical study report.				

Both Dr. Chowdhury and Ms. Liu recommend approval. Because it has been well established that omega-3 fatty acids lower serum TG levels and the results of the EVOLVE trial were statistically robust, I agree that the applicant has provided sufficient evidence to conclude that Epanova, at dosages of 2 g to 4 g/day, is effective in reducing fasting TG levels in patients with severe hypertriglyceridemia.

## 7. SAFETY

The overall safety database for Epanova consisted of 1343 patients treated with at least one dose of Epanova (all 2 grams or greater) in 10 clinical trials. Four trials involving 180 Epanova-treated subjects were clinical pharmacology trials, which I will not discuss further. Two placebo (olive oil)-controlled trials (EVOLVE and ESPRIT, the latter in statin-treated patients with TG levels  $\geq 200$  and  $< 500$  mg/dL) contributed to a pool of hypertriglyceridemic patients. In addition to the differences in baseline characteristics, the durations of the double-

blind treatment periods of these trials were different (12 weeks for EVOLVE, 6 weeks for ESPRIT), and Epanova 3 g/day was not studied in ESPRIT. EVOLVE had 399 patients in the safety population (300 Epanova, 99 placebo) and ESPRIT had 646 (431 Epanova, 215 placebo). Thus, collectively, 731 patients with hypertriglyceridemia of varying severity were exposed to Epanova and 314 to placebo. Last, supportive data were provided from 432 patients with Crohn's disease treated with Epanova 4 g/day from a previous development program. The Crohn's database consists of two placebo-controlled trials of 52- and 58-weeks duration (collectively, 376 treated with Epanova and 372 with placebo), a 25-subject open-label 52-week study, and an 81-subject open-label extension with duration up to 3 years.

Dr. Giovanni Cizza has reviewed the data from the overall Epanova safety database. In this memo, I will focus on the safety data from the two placebo-controlled trials involving hypertriglyceridemic patients, since these data are most relevant to the proposed indication. A total of 314 patients were exposed to placebo, 315 to Epanova 2 g/day, 101 to Epanova 3 g/day, and 315 to Epanova 4 g/day. The median number of days of drug exposure was 84 days in EVOLVE and 42 days in ESPRIT, yielding a median 43 days if both trials are pooled.

In addition to having different baseline TG levels, the study populations of EVOLVE and ESPRIT had other notable differences in baseline characteristics. Patients in ESPRIT had a median age that was roughly 10 years older than EVOLVE (~60 years vs. ~50 years), with the proportions of patients  $\geq 65$  years being ~40% vs. ~10% in ESPRIT and EVOLVE, respectively. In addition, in ESPRIT, there was a greater proportion of diabetics (72% vs. 38%), women (41% vs. 23%), and by design, statin  $\pm$  ezetimibe use (99.9% vs. 35%).

## **Deaths**

There were three deaths reported in the overall safety database, two in the Crohn's population (malignant melanoma in an Epanova-treated patient and metastatic adenocarcinoma in a placebo-treated patient), and one in the hypertriglyceridemic population ("pulmonary embolus" in an Epanova-treated patient). Regarding the malignant melanoma-related death, a 68-y/o woman with Crohn's was diagnosed with a malignant melanoma on her back, 129 days after starting Epanova 4 g/day. The subject completed the 52-week study without known recurrence, was diagnosed with liver metastases approximately 7 months after stopping study drug, and died within two months thereafter. Regarding the death in the EVOLVE trial, a 60-y/o man with a history of hypertriglyceridemia, hypertension, and diabetes mellitus is said to have had "sudden death" 11 days after starting Epanova 3 g/day; no autopsy was performed. The physician on duty "considered the cause of death pulmonary embolism." Although I believe there is insufficient evidence to conclude that this death was a result of pulmonary embolism, I agree with Dr. Cizza's conclusion that it is unlikely that this death, or the malignant melanoma, was related to Epanova.

### **Serious Adverse Events**

The incidence of nonfatal serious adverse events (SAEs) was low in EVOLVE and ESPRIT, with no suggestion of a higher risk with Epanova treatment. In EVOLVE, the incidence of nonfatal SAEs was 2.0% for placebo and 1.0%, 3.0%, and 0% for the Epanova 2 g, 3 g, and 4 g/day groups, respectively, yielding 1.3% overall for Epanova-treated patients. I have reviewed the narratives for these events. Of the 4 nonfatal SAEs in Epanova-treated patients in EVOLVE, two were hospitalizations for angina in patients with a history of ischemic heart disease on days 72 and 74, one was a hospitalization for chest pain on the same day that Epanova was started, and the last was a hospitalization for an upgrade to a biventricular ICD. In ESPRIT, the incidence of SAEs was 1.4% for placebo, 1.4% for Epanova 2 g/day, and 0.5% for Epanova 4 g/day, yielding 0.9% overall for Epanova-treated patients. Limited information was provided for these events, but I have reviewed the case report forms. The 4 nonfatal SAEs in Epanova-treated patients in ESPRIT were hospitalizations for musculoskeletal chest pain, perforated diverticulitis, a total left knee replacement (coded "osteoarthritis"), and "routine angiogram for insurance purposes" followed by scheduling bypass surgery two days later.

Thus, the hypertriglyceridemia trials had a pooled incidence of nonfatal SAEs of 1.6% (5/314) in the combined placebo groups and 1.1% (8/731) in the combined Epanova groups. I agree with Dr. Cizza that these trials do not suggest that treatment with Epanova 2 g to 4 g/day is associated with serious adverse events.

### **Adverse Events Leading to Discontinuation**

In EVOLVE, Dr. Cizza notes that 17 (5.7%) of 300 Epanova-treated patients discontinued as a result of nonfatal adverse events compared with none of the 99 placebo-treated patients. The number of events in the Epanova 2 g, 3 g, and 4 g/day groups were 5, 7, and 5, respectively. Nine of these events (3 per Epanova dose group) were gastrointestinal in nature (e.g., abdominal pain, nausea, vomiting, diarrhea). The remaining two events in the Epanova 4 g/day group were for worsening of diabetes, at topic that I will discuss later in this review. There was one adverse event that could be considered bleeding-related (menorrhagia) leading to discontinuation in the Epanova 3 g/day group. The remaining events in the Epanova 3 g group included 6 days of facial edema (without rash or shortness of breath) that started on the first day of drug administration; menorrhagia, which apparently resolved after two days of drug interruption but started again after taking an additional single dose; and two of the SAEs (hospitalizations for CAD and angina pectoris) described above. Last, the remaining two non-GI-related adverse events leading to discontinuation in the Epanova 2 g group were weight gain and urticaria.

In ESPRIT, adverse events leading to discontinuation occurred in 2 (0.9%) subjects in the placebo group, 3 (1.4%) in the Epanova 2 g group, and 7 (3.2%) in the Epanova 4 g group (i.e., 10 [2.3%] of all Epanova-treated patients). With the exception of two events, gastrointestinal events (e.g., nausea, vomiting, diarrhea, abdominal pain/bloating, belching, flatulence) were responsible for the Epanova-related discontinuations; the remaining two events were

described previously as SAEs (“osteoarthritis” and the patient scheduled for a routine angiogram who then had bypass surgery scheduled).

Thus, the hypertriglyceridemia trials had a pooled incidence of adverse events leading to discontinuation of 0.6% (2/314) in the combined placebo groups and 3.7% (27/731) in the combined Epanova groups, with the majority (17/27) of events in Epanova-treated patients being gastrointestinal in nature.

### Common Adverse Events

In his review, Dr. Cizza summarizes the adverse events that occurred in >1% of patients in either the pooled placebo or pooled Epanova groups (EVOLVE + ESPRIT). He notes that in both trials, the incidence of adverse events was more common in the pooled Epanova groups than the pooled placebo groups (EVOLVE: 41% vs. 26%; ESPRIT: 37% vs. 28%; EVOLVE+ESPRIT: 39% vs. 27%), and that the most commonly reported AEs were gastrointestinal (diarrhea, nausea, and eructation being the most common).

I used the adverse event datasets (*ae.xpt*) from both EVOLVE and ESPRIT to confirm adverse events that occurred with an incidence  $\geq 3\%$ , and numerically greater than placebo, in any Epanova-treatment group. I repeated this procedure with a pooled hypertriglyceridemia dataset and obtained results that were quite similar. The most common adverse events ( $\geq 3\%$ ) that occurred with greater frequency in at least one Epanova dose group compared with placebo are summarized below.

Adverse Event	Placebo (n=314)	Epanova 2g (n=315)	Epanova 3g (n=101)	Epanova 4g (n=315)
Diarrhea	7 (2%)	23 (7%)	6 (6%)	46 (15%)
Nausea	4 (1%)	12 (4%)	9 (9%)	18 (6%)
Abdominal Pain or Discomfort*	7 (2%)	11 (3%)	2 (2%)	15 (5%)
Eructation	1 (<1%)	9 (3%)	4 (4%)	10 (3%)
Vomiting	1 (<1%)	6 (2%)	4 (4%)	4 (1%)

Source: Clinical Team Leader's analysis from EVOLVE & ESPRIT *ae.xpt* datasets

\* For this analysis, the following observed preferred terms were combined: abdominal pain, abdominal pain upper, and abdominal discomfort.

I also combined the adverse event analysis datasets (*adae.xpt*) from the placebo-controlled Crohn's disease trials (EPIC-1 and EPIC-2)<sup>20</sup> and identified AEs that occurred with an incidence  $\geq 3\%$ , and numerically greater than placebo, with Epanova treatment. These events included abdominal pain, diarrhea, nausea, abdominal tenderness, abdominal distension, frequent bowel movements, constipation, vomiting, fatigue, asthenia, nasopharyngitis, bronchitis, arthralgia, back pain, and dysgeusia. Requiring a risk difference of 1% and eliminating the terms that are essentially included in the table above leaves the following additional potential adverse reactions from the controlled Crohn's disease trials: abdominal

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<sup>20</sup> This pool comprised 748 patients: 376 Epanova 4 g/day and 372 placebo.

distension, constipation, vomiting, fatigue, nasopharyngitis, arthralgia, and dysgeusia. As Dr. Cizza discusses in his review, AEs of dysgeusia relate to reports of a fishy taste.

### **Selected Safety Topics**

For this review, I will focus on three safety topics commonly addressed for drugs that contain omega-3 fatty acids: increases in bleeding as a result of potential modulation of platelet aggregation, increases in glucose levels, and increases in hepatic transaminases. Unless otherwise stated, these analyses all refer to the hypertriglyceridemia trials, EVOLVE and ESPRIT.

#### ***Bleeding***

As stated in labeling for Lovaza, Vascepa, and Omtryg, some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients taking these treatments and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

Patients taking anticoagulants, including clopidogrel, were excluded from EVOLVE and ESPRIT, limiting the safety evaluation of the concomitant administration of Epanova with these agents.

The applicant identified potential bleeding and hemorrhagic AEs using the broad Standardized MedDRA Query (SMQ) for hemorrhage, and Dr. Cizza summarized these results in his review. I conducted my own analysis using the Hemorrhage SMQ and the EVOLVE and ESPRIT AE datasets (*ae.xpt*), and I identified one additional “contusion” AE in the Epanova 3 g/day group of EVOLVE. In EVOLVE, the broad Hemorrhage SMQ identified 7 (2.3%) of 300 Epanova-treated subjects (8 events) and none in the placebo group. In ESPRIT, the broad Hemorrhage SMQ identified 3 (0.7%) of 431 Epanova-treated subjects (4 events) and 3 (1.4%) of 215 in the placebo group. Thus, in the pooled hypertriglyceridemia dataset, the incidence of potential bleeding-related AEs identified solely by the broad Hemorrhage SMQ was 10 (1.4%) vs. 3 (1.0%) in the pooled Epanova and placebo groups, respectively.

Of these 13 subjects with at least one Hemorrhage SMQ event, none had SAEs, one led to drug withdrawal (the case of menorrhagia described previously; Epanova 3 g/day group), and none had an event described as severe in intensity. By treatment group, there were 2 subjects (0.6%) who received Epanova 2 g/day (worsening internal hemorrhoidal bleeding; hematuria), four subjects (4.0%) who received Epanova 3 g/day (menorrhagia; bruising to left arm; contusion of left knee; increased PTT), and four subjects (1.3%) who received Epanova 4 g/day (two with both decreased Hgb and decreased Hct; and one each with increased INR and positive fecal occult blood test). The three placebo subjects (1.0%) reported increased bleeding when cut finger, bilateral 5<sup>th</sup> toe contusion secondary to fall, and hematuria.

Regarding laboratory data, in the pooled database of EVOLVE and ESPRIT, the mean (SD) change in hemoglobin from baseline to final observation was 0.0 (0.70) g/dL for the 643 Epanova-treated subjects with available data and 0.0 (0.59) g/dL for the 283 placebo-treated subjects with available data. The mean (SD) change in hematocrit from baseline to final observation was -0.4% (2.14) for the Epanova-treated subjects and -0.5% (1.98) for the placebo-treated subjects. Results were similar for EVOLVE and ESPRIT considered separately.

Dr. Cizza noted that there were two subjects, both in an Epanova group, with grade 2 hemoglobin (i.e.,  $\geq 8.0$  to  $< 10.0$  g/dL), although my review of the applicant's shift tables found that these subjects had grade 2 hemoglobin at baseline as well.<sup>21</sup> Using the combined EVOLVE + ESPRIT hypertriglyceridemia pool, I calculated that the proportions of subjects with at least one post-baseline hemoglobin value who shifted to a more-severe grade were 6.0%, 6.0%, 3.7%, and 6.8% for the placebo and Epanova 2 g, 3 g, and 4 g/day groups, respectively.<sup>22</sup> No patient shifted more than one grade.

In Dr. Cizza's review, he also notes that the supporting trials in the Crohn's disease population did not suggest a propensity for bleeding based on the identification of potential bleeding-related events with the broad Hemorrhage SMQ discussed previously. Although the incidence of events was higher, likely attributable to the population studied, the proportions of patients who reported an AE included in the Hemorrhage SMQ were 8.6% for the Epanova 4 g/day group and 8.3% for placebo. The majority of these events were rectal hemorrhage and hematochezia, as one might expect with Crohn's disease. Regardless, the similarity between treatment groups in a population with a propensity for gastrointestinal bleeding is somewhat reassuring.

Taken together, I conclude that the current Epanova safety database does not suggest that Epanova promotes bleeding.

### *Hyperglycemia*

The applicant identified potential adverse events related to hyperglycemia using the broad SMQ for Hyperglycemia/New Onset Diabetes (hereafter, "Hyperglycemia SMQ"), and Dr. Cizza summarized these results in his review. I conducted my own analysis using this SMQ and obtained the same results as the applicant. In EVOLVE, the broad Hyperglycemia SMQ identified 11 (3.7%) of 300 Epanova-treated subjects (14 events) and 5 (5.1%) of 99 in the placebo group (6 events). In ESPRIT, the broad Hyperglycemia SMQ identified 11 (2.6%) of 431 Epanova-treated subjects (11 events) and 5 (2.3%) of 215 in the placebo group (5 events). Thus, in the pooled hypertriglyceridemia dataset, the incidence of potential

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<sup>21</sup> ISS Table 4.8.1.1 "Summary of Hematology Laboratory Shifts by Maximum NCI-CTC Grade." Grade 0: above LLN; grade 1:  $\geq 10$  g/dL but  $< LLN$ ; grade 2:  $\geq 8.0$  but  $< 10$  g/dL. No patients had hemoglobin values more severe than grade 2.

<sup>22</sup> Missing data for approximately 11%, 12%, 25%, and 13% for the placebo and Epanova 2 g, 3 g, and 4 g/day groups, respectively.

hyperglycemia/diabetes-related AEs identified solely by the broad Hyperglycemia SMQ was 22 (3.0%) vs. 10 (3.2%) in the pooled Epanova and placebo groups, respectively.

Several of the adverse events identified with the broad Hyperglycemia SMQ, however, were unlikely related to worsening diabetes control, especially given the population: e.g., in EVOLVE, there were 5 events (from 4 subjects) for worsening of triglycerides/hyperlipidemia in the placebo group. Furthermore, in this population, changes in weight (whether gain or loss) are unlikely to signal worsening glycemic control. Thus, I also analyzed the adverse event datasets (*ae.xpt*) from both trials for the corresponding narrow SMQ.<sup>23</sup> The resulting preferred terms that were observed in the EVOLVE+ESPRIT pool were: blood glucose increased, glycosylated hemoglobin increased, diabetes mellitus inadequate control, type 2 diabetes mellitus, diabetes mellitus, hyperglycemia, and glycosuria. As shown in the following table, from Table 38 (p. 63) in Dr. Cizza's review with minor modifications based on my independent review of the primary data, the incidence of adverse events in the narrow Hyperglycemia SMQ for the pooled hypertriglyceridemia trials was 1.9% for placebo and 1.6%, 2.0%, and 3.2% for the Epanova 2 g, 3 g, and 4 g/day groups, respectively.

Preferred Term	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) <sup>a</sup>	2 (0.6) <sup>b</sup>
Glycosylated hemoglobin increased	0	2 (0.6)	0	1 (0.3) <sup>b</sup>
Glycosuria	0	0	1 (1.0) <sup>a</sup>	0
<b>Total Subjects</b>	<b>6 (1.9)</b>	<b>5 (1.6)</b>	<b>2 (2.0)</b>	<b>10 (3.2)</b>

Superscripts of the same letter represent adverse events from the same subject.

\* Verbatim terms indicating a *worsening* of diabetes mellitus were coded to the preferred term "Diabetes mellitus." Verbatim terms for two patients simply stated "Diabetes mellitus type 2" and were coded to the same preferred term. I could not find evidence in the medical history dataset (*mh.xpt*) that these latter two patients had an established diagnosis of diabetes prior to the trial.

Furthermore, in EVOLVE, the number of subjects with at least one of these events in the placebo and Epanova 2 g, 3 g, and 4 g groups were 1, 1, 2, and 5, respectively. In ESPRIT, the number of subjects with at least one of these events in the placebo, Epanova 2 g, and Epanova 4 g groups were 5, 4, and 5, respectively. These results were sent to the applicant as part of an information request on 26 March 2014, also noting that given that these events could be time-dependent, the similar incidence of the events across groups in the 6-week ESPRIT trial was not particularly reassuring. We noted that all of the events in EVOLVE were reported on Days 85-92, with the exception of one patient in the Epanova 4 g/day group who had a date of onset of "worsening of diabetes mellitus" on day 65, which was an AE that led to drug

<sup>23</sup> In this dataset, compared with the broad SMQ, the narrow SMQ eliminated the following preferred terms: weight increased, weight decreased, blood triglycerides increased, hyperlipidemia, and increased appetite.

discontinuation. The applicant was asked to confirm these results, comment on their interpretation, and provide results for changes in central tendency for glucose and HbA1c from baseline by diabetes status.

The applicant responded to this request in an amendment received 16 April 2014, data from which are included in Dr. Cizza's review. The applicant noted that subjects exhibiting these AEs either had a history of type 2 diabetes and/or presented with clinical laboratory assessments consistent with diabetes at screening. In addition, the applicant reasonably pointed out that, by design, the laboratory results used by investigators to determine a diabetes-associated AE were scheduled to be collected only twice: screening and end of treatment (day 84 in EVOLVE, day 42 in ESPRIT); therefore, the clustering of AEs at the end of the trial does not suggest time dependence. Furthermore, they stated that although the Epanova 4 g/day group had a few more subjects reporting a diabetes-associated AE than the other groups, examination of the laboratory findings show that one of these subjects had screening and end-of-treatment HbA1c values of 8.3% and 7.9%, respectively, and another had values of 6.2% and 6.3%. In the Epanova 3 g/day group, one of the subjects had HbA1c values of 7.1% at screening and 6.3% at end of treatment, the other subject had values of 7.1% and 7.5%.

Regarding laboratory data among all patients, Dr. Cizza presents the measures of central tendency for both fasting glucose and HbA1c, at baseline and end of treatment, for the EVOLVE and ESPRIT trials. These data do not suggest a drug- or dose-related effect on glycemic control in these trials. To supplement the data presented in his review, combining EVOLVE and ESPRIT, the absolute mean changes in fasting glucose from baseline to final observation were +1.5 mg/dL for 683 pooled Epanova-treated patients and +1.5 mg/dL for 302 pooled placebo patients.<sup>24</sup> Given the 6-week duration of ESPRIT, I will only present changes in HbA1c measured in EVOLVE: the mean absolute change in % HbA1c from baseline to end of treatment was +0.1% in the placebo group and +0.2%, +0.1%, and +0.1% in the Epanova 2 g, 3 g, and 4 g/day groups, respectively.

As noted previously, data regarding changes in fasting glucose and HbA1c by diabetes status were requested from the applicant. For these analyses, the applicant diagnosed diabetes at baseline as a history of diabetes, use of antidiabetic medication, or HbA1c  $\geq 6.5\%$ . Dr. Cizza presents these data in his review for EVOLVE, ESPRIT, and the trials combined. To complement the data he included, I note that the applicant included estimated median differences (Hodges-Lehmann) between Epanova dose groups and placebo for the changes in these variables from baseline to end of treatment. I have presented these data in the table below.

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<sup>24</sup> ISS Table 4.1.1.1 "Serum Chemistry"

	Median Difference [Hodges-Lehmann] (95% CI)		
	Epanova 2g vs. Pbo	Epanova 3g vs. Pbo	Epanova 4g vs. Pbo
<b>EVOLVE</b>			
<b>Fasting Glucose (mg/dL)</b>			
With Diabetes	-2.5 (-19.0, +14.0)	-0.5 (-19.0, +20.0)	-9.0 (-31.0, +10.0)
Without Diabetes	-1.0 (-5.0, +3.0)	+2.0 (-1.0, +6.0)	+2.0 (-2.0, +6.0)
<b>Hemoglobin A1c (%)</b>			
With Diabetes	+0.1 (-0.3, +0.4)	0.0 (-0.3, +0.3)	+0.1 (-0.2, +0.4)
Without Diabetes	0.0 (-0.1, +0.1)	0.0 (-0.1, +0.1)	0.0 (-0.1, 0.0)
<b>ESPRIT</b>			
<b>Fasting Glucose (mg/dL)</b>			
With Diabetes	-1.0 (-7.0, +4.0)	N/A	+2.0 (-3.0, +7.0)
Without Diabetes	+1.0 (-2.0, +5.0)	N/A	0.0 (-3.0, +3.0)
<b>Hemoglobin A1c (%)</b>			
With Diabetes	0.0 (-0.1, +0.1)	N/A	0.0 (-0.1, +0.1)
Without Diabetes	0.0 (-0.1, +0.1)	N/A	0.0 (-0.1, +0.1)

Source: 16 April 2014 response to information request, Tables 1.11.2-2, 1.11.2-3, 1.11.2-5, and 1.11.2-6.  
 For EVOLVE, Epanova 2 g, 3 g, and 4 g groups had n=34, 38, and 35 (with diabetes) and n=59, 47, and 56 (without diabetes), respectively, with end-of-treatment values.  
 For ESPRIT, Epanova 2 g and 4 g groups had n=144 and 133 (diabetes) and n=54 and 62 (without diabetes), respectively, with end-of-treatment values.

Dr. Cizza commented that these exploratory analyses were triggered by a numerical difference observed in AEs potentially representing worsening of diabetes between the placebo group and the Epanova 4 g/day group in EVOLVE (1.0% vs. 5.1%). He concluded that these analyses do not support “the existence of a relationship between Epanova 4 g and type 2 diabetes” (p. 70). I agree that these data are reassuring.

Shift tables for glucose were reviewed by Dr. Cizza, and he concluded that “[t]he numbers are too small to attempt any inference on whether treatment with Epanova changes the proportion of subjects with high fasting glucose” (p. 85). Using the combined EVOLVE + ESPRIT hypertriglyceridemia pool, I calculated that the proportions of subjects with at least one post-baseline glucose value who shifted to a more-severe grade were 15.2%, 16.6%, 18.8%, and 15.8% for the placebo and Epanova 2 g, 3 g, and 4 g/day groups, respectively.<sup>25</sup>

<sup>25</sup> Blood glucose grade 0: <ULN; grade 1: ULN to ≤160 mg/dL; grade 2: >160 to ≤250 mg/dL; grade 3: >250 to ≤500 mg/dL. Missing data for approximately 4%, 5%, 19%, and 6% for the placebo and Epanova 2 g, 3 g, and 4 g/day groups, respectively.

Taken together, I believe that it is reasonable to conclude that the current Epanova safety database does not suggest that Epanova worsens glycemic control, although I agree with Dr. Cizza that the relatively small number of patients and short duration of the trials are limitations.

### *Liver-related Safety*

There were no cases of Hy's Law or fulminant hepatic failure in the Epanova safety database. In both EVOLVE and ESPRIT, liver-related laboratory assessments were only performed at Week -2 and at the end of treatment.

In his review, Dr. Cizza presented the changes in central tendency for ALT and AST for pooled Epanova dose groups and placebo for EVOLVE, ESPRIT, and trials combined. Four subjects in the combined hypertriglyceridemia pool had post-baseline ALT values >3xULN: 2 (0.6%) in the combined placebo group and 0, 1 (1.2%), and 1 (0.3%) in the Epanova 2 g, 3 g, and 4 g/day groups, respectively. Both of the Epanova-treated patients had elevated ALT at baseline.<sup>26</sup> There were no elevations in bilirubin to >2x ULN.

To supplement the data presented in Dr. Cizza's review, I considered subjects who had normal ALT values and baseline and determined the incidence of any ALT elevation above ULN. This occurred in 18/224 (8.0%) and 88/499 (17.6%) of placebo- and Epanova-treated patients, respectively (chi-square P=0.0007). Considering subjects who had baseline ALT values >ULN but ≤3xULN, 1/68 (1.5%) and 2/166 (1.2%) of placebo- and Epanova-treated patients, respectively, had follow-up values >3xULN, and 27 (39.7%) and 36 (21.7%), respectively, had maximum post-baseline values that had fallen below the ULN.<sup>27</sup> Thus, I would conclude that Epanova is associated with modest increases in ALT in some patients.<sup>28</sup>

Although AST is less specific for liver-related abnormalities than ALT, I also calculated the proportions of patients with elevations in AST. Only considering subjects who had normal AST at baseline in the EVOLVE+ESPRIT hypertriglyceridemia pool, 21/237 (8.9%) and 65/521 (12.5%) of placebo- and Epanova-treated patients, respectively, had a post-baseline AST elevation above ULN (chi-square P=0.15); one of the placebo subjects had a maximum AST >3xULN. Considering subjects who had baseline AST values >ULN but ≤3xULN, 1/56 (1.8%) and 2/144 (1.4%) of placebo- and Epanova-treated patients, respectively, had follow-up values >3xULN, and 27 (48.2%) and 47 (32.6%), respectively, had maximum post-baseline values that

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<sup>26</sup> Subject 136-006 (Epanova 3 g) had an ALT 81 U/L (2.0x ULN) at Week -2, which rose to 157 U/L (3.8x ULN) at end of treatment (AST values were 72 and 120 U/L, respectively); and Subject 013-029 (Epanova 4 g) had an AST 101 U/L (2.5xULN) at Week -2, which rose to 167 U/L (4.1x ULN) at end of treatment (AST values were 47 and 79 U/L, respectively).

<sup>27</sup> ISS Table 4.7.2.1

<sup>28</sup> The pattern of modest ALT elevations was qualitatively similar in both EVOLVE and ESPRIT. Only considering those with normal ALT at baseline, the numbers of subjects with maximum post-baseline ALT >ULN in EVOLVE were 12/65 (18.5%) and 42/189 (22.2%) in the placebo and pooled Epanova groups, respectively; in ESPRIT, 6/159 (3.8%) and 46/310 (14.8%) in the placebo and pooled Epanova groups, respectively.

had fallen below the ULN. Although I do not find these data as compelling as ALT, Epanova may be associated with modest increases in AST in some patients.

In the pool of studies in the Crohn's disease population in which treatment duration was longer, there were no Epanova-treated subjects who had a post-baseline ALT >3xULN.<sup>29</sup>

Taken together, Dr. Cizza concludes that there is no evidence for a liver-related safety signal in the Epanova database. I agree that there is not a particularly worrisome signal, although there does appear to be a higher proportion of modest rises in ALT among Epanova-treated patients. Thus, similar to previous labels for fish oil-derived products, it is not unreasonable to recommend monitoring of transaminases for patients with hepatic impairment. I realize, however, that hepatic impairment is not defined by transaminase abnormalities but rather assessments of liver function, that there were no patients with hepatic impairment in the Epanova trials, and that monitoring transaminases would be expected to be routine clinical practice in such patients. Nevertheless, the changes in transaminases observed with Epanova are not any more or less concerning than previously approved products, so maintaining consistency in labeling seems appropriate.

In sum, Dr. Cizza recommends approval of Epanova 2 g and 4 g/day. I agree that there are no outstanding safety concerns that would preclude approval.

## **8. ADVISORY COMMITTEE MEETING**

Given the Division's experience with fish oil-derived products indicated for severe hypertriglyceridemia, it was determined that an advisory committee meeting was not necessary for this application.

## **9. PEDIATRICS**

The Division recommends that the Epanova application receive a full waiver for pediatric patients because the necessary studies would be impossible or highly impractical given the relatively small number of pediatric patients with TG levels  $\geq 500$  mg/dL.

## **10. OTHER RELEVANT REGULATORY ISSUES**

### **Financial Disclosure**

Dr. Chowdhury notes in her review the absence of financial interests and arrangements between the applicant and clinical investigators of the EVOLVE trial.

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<sup>29</sup> ISS Table 4.7.3.1

## Clinical Inspections

The Office of Scientific Investigations conducted routine pre-approval clinical inspections for data validation. Four clinical sites from the phase 3 pivotal trial (OM-EPA-003) and the sponsor (Omthera Pharmaceuticals, Inc.) were inspected. In her clinical inspection summary, Dr. Kleppinger concludes that “[i]n general, based on the inspections of the four clinical study sites and the sponsor, the inspectional findings support validity of the data as reported by the sponsor under this NDA.”

## Proprietary Name Review

The Division of Medication Error Prevention and Analysis and the Office of Prescription Drug Promotion concluded that the proposed proprietary name, Epanova, is acceptable from a safety and promotional perspective.

# 11. LABELING

The Division has negotiated labeling with the applicant. Some notable agreements include:

- The indication will read, “EPANOVA (omega-3-carboxylic acids) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$  mg/dL) hypertriglyceridemia.”
- Limitations of use will not specify the indicated population. They will read, “The effect of EPANOVA on the risk for pancreatitis has not been determined. The effect of EPANOVA on cardiovascular mortality and morbidity has not been determined.” This is consistent with the labeling recently approved for Omtryg and reflects the fact that the effect of the drug on these clinical outcomes is unknown for any population.
- Dosage and Administration will read, “The dosage of EPANOVA is 2 grams (2 capsules) or 4 grams (4 capsules) once daily. The dosage should be individualized according to the patient’s response and tolerability. In clinical trials, EPANOVA was administered without regard to meals.”
- Recommendations to monitor LDL-C and hepatic transaminases will be consistent with other labels of fish oil-derived products.
- Because the 3-gram dose is not being recommended in Dosage and Administration (no clear incremental benefit with regard to efficacy but not as well tolerated), results from the Epanova 3 g/day dosage group will not be included in Adverse Reactions or the Clinical Studies section. The exclusion of these data do not meaningfully affect the information provided for prescribers in labeling.
- Because there are nonclinical data that inform Section 8.2 (Labor and Delivery), these data will be added to the Epanova labeling but are not appropriate for other labels of fish oil-derived products.
- (b) (4), which is not recognized as a clinically meaningful outcome by itself. The approval of a 2 g/day dosage

- recommendation provides the clinically relevant distinction between this product and other currently approved fish oil-derived products.
- Within-group median % change from baseline for relevant lipid/lipoprotein parameters will be displayed in Section 14 along with the estimated between-group treatment difference to placebo (olive oil) using Hodges-Lehmann estimates. Notation for statistical significance will identify P values generated by the applicant's primary analysis (ANCOVA model using rank-transformed data).

Last, the applicant has indicated that they wish to (b) (4)  
The Division has informed them that we would view this as a (b) (4)  
(b) (4), and that this would require discussion with  
(b) (4), which we did not feel was appropriate while this NDA was under review. A  
path forward, (b) (4) has been  
provided for the applicant to pursue (b) (4) following approval.

## 12. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

Because the results of the EVOLVE trial were statistically robust and it has been well established that some fish oil-derived mixtures that contain omega-3 fatty acids can lower serum TG levels, I believe that the applicant has provided sufficient evidence to conclude that Epanova, at dosages of 2 g to 4 g/day, is effective in reducing fasting TG levels in patients with severe hypertriglyceridemia. The within-group median changes in TG from baseline to end of treatment were approximately -25% and -31% for Epanova 2 g and 4 g/day, respectively, and -10% for placebo (olive oil). Although the point estimates for the between-group differences vary slightly based on the statistical technique applied, the review team and I have no doubt that Epanova lowers TG. The treatment differences to be described in labeling (estimated median difference in % change) are -16% for Epanova 2 g/day and -21% for Epanova 4 g/day. Although it is not known with certainty whether Epanova-induced reductions of TG will result in improved clinical outcomes, the Division has never required an applicant to demonstrate a statistically significant reduction in the incidence of pancreatitis, given the relative rarity of hypertriglyceridemia-induced pancreatitis, before granting approval of a TG-lowering drug for this population. Thus, given that the safety profile of Epanova has not raised concerns and appears qualitatively similar to that observed for other fish oil-derived products and the published literature, I believe that the applicant has provided sufficient evidence that the benefit/risk profiles of Epanova 2 g/day and 4 g/day are favorable for the treatment of severe hypertriglyceridemia.

I agree with the review team that this application should be approved.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JAMES P SMITH  
05/05/2014

ERIC C COLMAN  
05/05/2014