

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205060Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA:	205060
Submission Date(s):	July 05, 2013
Brand Name	Epanova
Generic Name	Omefas
OCP Division	Clinical Pharmacology -2
OND division	Metabolism and Endocrinology Products
Sponsor	Omthera Pharmaceuticals
Submission Type; Code	NDA 505(b)(1); Standard
Formulation; Strength(s)	Soft gelatin capsules: <ul style="list-style-type: none"> • 1 g
Proposed Indication	<ul style="list-style-type: none"> • Adjunct to diet to reduce triglyceride (TG), ^{(b) (4)} levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.
Proposed Dosage & Administration	<ul style="list-style-type: none"> • The ^{(b) (4)} daily dose of EPANOVA is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules). • ^{(b) (4)} the daily dosage may be ^{(b) (4)} 4 grams per day, taken as a single 4-gram dose (4 capsules).
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1 Executive Summary

Epanova being developed by Omthera Pharmaceuticals is a mixture of polyunsaturated free fatty acids (PUFAs) derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids.

Epanova is intended as an adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia

If approved, Epanova will be the third PUFA to enter the market. The other two approved products are (a) Lovaza, which has a combination of ethyl esters of omega 3 fatty acids, principally EPA and DHA (containing approximately 465 mg EPA and 375 mg DHA in each 1g capsule) and a (b) (4) percentage ((b) (4)%) of a mixture other oils such as (b) (4), and (b) Vascepa, which contains 1gm of ethly ester of EPA per capsule. The esterified form of EPA and DHA have to be de-esterified prior to absorption. The main advantage with Epanova formulation is the availability of EPA and DHA as free fatty acids, thereby eliminating the de-esterification step in the absorption process. Under low fat conditions, and to some extent under high-fat conditions, there is a higher bioavailability of EPA and DHA from Epanova. Epanova also contains a (b) (4) percentage ((b) (4)%) of DPA compared to the quantity of DPA in Lovaza.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology data submitted on 07/05/13 under NDA 205060 and recommend approval with the following recommendations.

- Recommended daily dose of EPANOVA is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules)
- Maximum daily dose should not exceed 4-grams (4 capsules).
- OCP recommends that frequent monitoring of INR in patients on warfarin and/or coumarin derivatives, as well as following of instructions in the warfarin product monograph for appropriate monitoring and dose adjustment is recommended at the time of initiation or ending of Epanova treatment.

In lieu of a briefing meeting, a briefing summary document was distributed to the Senior Leadership in the Office of Clinical Pharmacology on March 26, 2014

1.2 Phase IV Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

The Epanova formulation is a soft gelatin oblong capsule containing 1,000 mg of drug substance (omefas) and coated with a red/brown pigmented polymeric coat. Each capsule contains not less than 850 mg of polyunsaturated fatty acids. The predominant omega-3 fatty

acids are eicosapentaenoic acid (EPA 500-600 mg), docosahexaenoic acid (DHA 150-250 mg) and docosapentaenoic acid (DPA (b) (4) mg).

The (b) (4) daily dose of Epanova is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules). (b) (4) the daily dosage may be (b) (4) 4 grams per day, taken as a single 4-gram dose (4 capsules).

Key pharmacokinetic properties of Epanova are summarized in [Table 1](#).

Table 1 Highlights of Pharmacokinetics

Proposed dose	<ul style="list-style-type: none"> • (b) (4) 2 g/day as a single dose; • (b) (4) 4 g/day as a single dose
Absorption	<ul style="list-style-type: none"> • Linear pharmacokinetics between 2 g and 8 g doses • Median T_{max} - EPA: ~ 4.5 – 5.5 h; DHA: 4.7 – 5.3 hrs • t_{1/2} - EPA: 4.7 – 10.8 h; DHA: ~7 h • Mean EPA and DHA trough levels similar at 16 and 52 weeks of daily dosing of 4 g Epanova • approximate 2-fold accumulation of EPA during continued dosing • Steady-state concentrations achieved within 2 weeks of 4 g once-daily dosing
Distribution	<ul style="list-style-type: none"> • 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.
Metabolism and Elimination	<ul style="list-style-type: none"> • 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.

1.3.1 Dose-response relationship for efficacy

Triglyceride Lowering:

The sponsor studied three doses (2 g/day, 3g/day and 4g/day) of Epanova in the pivotal Phase 3 trial. Though Epanova capsule contains a mixture of EPA, DHA and DPA, only EPA and DHA were quantitated in the clinical trials. The contribution of DPA towards efficacy or safety if any, is unknown. No clear dose response relationship between TG lowering and EPA or DHA exposure was observed ([Figure 1](#) and [Figure 2](#), respectively).

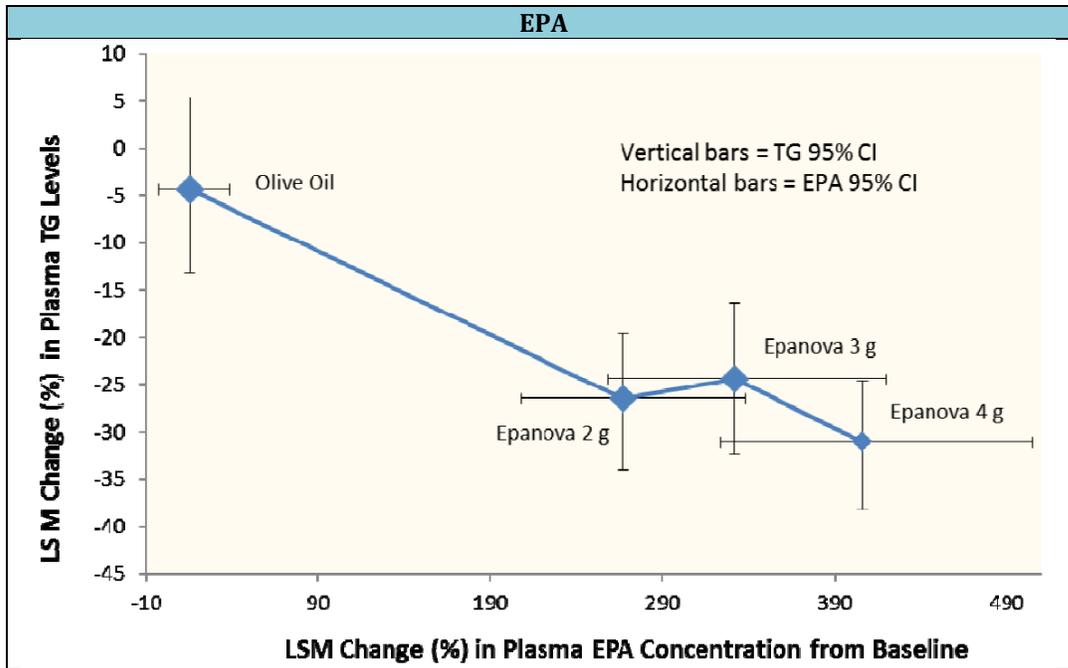


Figure 1 Least Square Mean (LSM) Change (%) in Plasma TG Levels vs. LSM Change (%) in Plasma EPA Concentration from Baseline

(Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 2.7.2-22, Page 47)

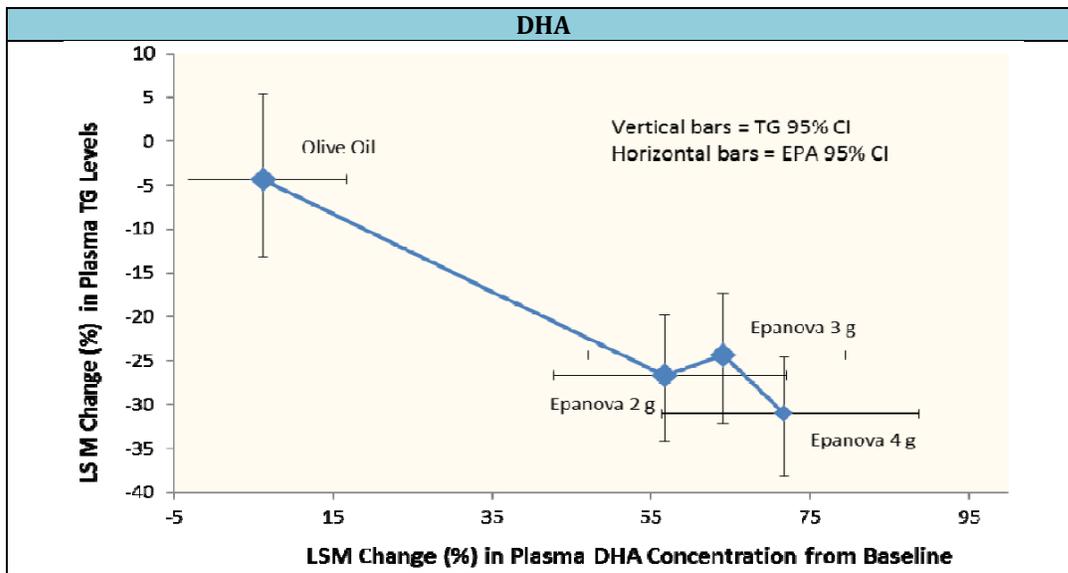


Figure 2 Least Square Mean (LSM) Change (%) in Plasma TG Levels vs. LSM Change (%) in Plasma DHA Concentration from Baseline

(Source: Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 2.7.2-22, Page 47)

1.3.2 *Intrinsic Factors*

- Age: No clinically relevant effect on the pharmacokinetics of EPA or DHA
- Gender: No clinically relevant effect on the pharmacokinetics of EPA or DHA
- Race: No clinically relevant effect on the pharmacokinetics of EPA or DHA
- Body weight: No clinically relevant effect on EPA or DHA
- Renal and Hepatic impairment: not studied

The observations of intrinsic factors on the pharmacokinetics of EPA or DHA is similar to what is known for this product class.

1.3.3 *Drug-Drug Interactions:*

- **Simvastatin:** Daily coadministration of simvastatin 40 mg with Epanova 4 grams did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or the major active metabolite, beta-hydroxy simvastatin at steady state.
- **Aspirin:** The anti-platelet effect of low-dose aspirin is not altered by the concomitant administration of Epanova. The mean VerifyNow aspirin assay results for simvastatin+aspirin+Epanova were comparable to the mean results for simvastatin+aspirin. The values following both treatments are consistent with those from patients receiving the antiplatelet effect of aspirin (ARU<550). The post-treatment decreases, with respect to baseline of 216 ARU and 211 ARU following simvastatin+aspirin+Epanova and following simvastatin+aspirin, respectively, were comparable ($p>0.05$).
- **Warfarin:** At steady-state, Epanova 4 grams/day did not significantly change the single dose AUC or C_{max} of R- and S- warfarin or the anti-coagulation pharmacodynamics of 25 mg warfarin.

1.3.3.1 *Specific Population*

1.3.3.1.1 *Hepatic Impairment*

Epanova has not been studied in patients with hepatic impairment.

1.3.3.1.2 *Renal Impairment*

Epanova has not been studied in patients with renal impairment.

2 Question-Based Review (QBR)

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical studies with PK and/or PD information submitted in the NDA

The clinical pharmacology program performed to evaluate the pharmacokinetic and pharmacodynamic properties of Epanova included 5 clinical pharmacology trials.

These comprised 2 Phase 1 trials in healthy subjects (including multiple-dose comparison to Lovaza, drug-drug interaction with simvastatin, warfarin and aspirin), 1 Phase 2 trial in healthy subjects to compare the bioavailability of EPA and DHA from Epanova and lovaza, and 2 Phase 3 studies from which PK data were available.

There were 5 supportive studies (1 Phase 1 study in healthy subjects to evaluate dose-proportionality, 1 Phase 2 study in Crohn's disease patients to evaluate the safety, pharmacokinetics and pharmacodynamics, and 3 Phase 3 studies in Crohn's disease patients to evaluate safety and efficacy of Epanova.

The program was supported by 2 human biomaterial studies, which have been conducted to provide supporting information on the clinical pharmacology of Epanova ([Table 2](#)).

These *in vitro* studies investigated the influence of Epanova on the *in vitro* permeation of Methotrexate across Caco-2 cell monolayer, and the inhibition of cytochrome P-450 Isoenzymes -2B6, 2C8, and 2C9. A list of all completed clinical pharmacology studies is provided in [Table 3](#).

Table 2 Overview of human biomaterial studies with Epanova

Study Type	Document number	Biomaterial	Test Concentration
Permeability Study	033-00	Caco-2 cell monolayer	5 µM, 10 µM and 100 µM
CYP Inhibition potential	03101701	Human Liver Microsomes	10 µM, 200 µM
CYP Inhibition potential	300101	Human Liver Microsomes	0.1 µM, 1 µM and 10 µM

Table 3 Overview of studies with pharmacokinetic and pharmacodynamic assessments relevant to the clinical pharmacology of Epanova

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase II PK/BA	Study OM-EPA-001	To compare the bioavailability of EPA and DHA, assessed by measurement of the AUC in plasma, after fasting and a high-fat meal, from a single 4 g dose of Epanova and Lovaza.	Randomized, open-label, 4-way crossover study, with 4 single-dose treatment periods and a 7-day washout in between each treatment	Epanova 4g x 2 (a.m. fasted and highfat meal) Lovaza 4g x 2 (a.m. fasted and high-fat meal) 2 single dose of each of Epanova and Lovaza	54	Healthy M or F, age ≥ 18 years	Single dose
Phase I PK/PD /BA	Study OM-EPA-006	To determine the effect of multiple doses of Epanova on the pharmacokinetic and anti-coagulant activity of single dose warfarin and to compare the systemic exposure of total EPA, total DHA, and total EPA+DHA following multiple-dose administration of Epanova compared to multiple-dose administration of Lovaza (omega-3 acid ethyl esters).	Open-label, 2-cohort, parallel design	Cohort 1: Treatment A: Single dose of warfarin w/o Epanova Treatment B: Single dose of warfarin with 4g QD Epanova Cohort 2: Treatment C: 4g QD of Lovaza following low fat breakfast	52 subjects enrolled 26 enrolled in Epanova cohort 26 enrolled in Lovaza cohort	Healthy M or F, age 18-55 years	21 days for Cohort 1, 14 days for Cohort 2
Phase I PK/BA	Study OMEPA-007	To determine effect of multiple doses of Epanova on multiple-dose PK of simvastatin.	Open label 2-way crossover study with 2 week washout between treatments; no comparator	Treatment A: 40mg simvastatin; 81mg of aspirin, and 4g of Epanova Treatment B: 40mg of simvastatin and 81mg of aspirin	52	Healthy M or F, age 18-55 years	Treatment A; 14 days Treatment B: 14 days
Phase III Efficacy	Study OMEPA-003	To evaluate the efficacy and safety of	Randomized, double blind, olive	Epanova 2g QD arm (n=100)	399	M or F, age ≥18 years, with serum	12 weeks

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PK/PD		Epanova in severe hypertriglyceridemic subjects	oil controlled, parallel group design	Epanova 3g QD arm (n=101) Epanova 4g QD arm (n=99) Olive oil (placebo) QD arm (n=99)		TG values at screening in the range ≥ 500 mg/dL and < 2000 mg/dL	
Phase I	Study SPC-275-4	Evaluation of the tolerability and safety and PK of multiple increasing oral doses of Epanova.	Randomized, placebo and active controlled, multiple dose study	Epanova 2g/d (1 g BID) 4g/d (2 g BID) 8 g/d (4g BID) 4.5 g/day ^(b) (2 g QD + 2.5 g QD) MaxEpa (fish oil) 9 g/day (4 g QD + 5 g QD) Placebo (triglyceride saturated fatty acids) 8 g/d (4 g BID)	73	Healthy M or F, age 18-60. years	42 days (6 weeks)

(Source: Epanova NDA eCTD module 5.2; Tables 5.2-1 and 5.2-2, pages 2-7)

The clinical program performed to evaluate the efficacy and safety of Epanova included 1 Phase 3 trial. Reduction in triglyceride (TG) levels was the primary endpoint in this study. In addition, the efficacy and safety of adding Epanova to statin therapy was evaluated in another Phase 3 trial. A listing of Phase 3 studies (pivotal and supportive) with Epanova is presented in [Table 4](#).

Table 4 Clinical Phase 3 studies with Epanova

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Phase III Efficacy PK/PD	Study OM-EPA-003	To evaluate the efficacy and safety of Epanova in severe hypertriglyceridemic subjects	Randomized, double blind, olive oil controlled, parallel group design	Epanova 2g QD arm (n=100) Epanova 3g QD arm (n=101) Epanova 4g QD arm (n=99) Olive oil (placebo) QD arm (n=99)	399	M or F, age ≥18 years, with serum TG values at screening in the range ≥500 mg/dL and <2000 mg/dL	12 weeks
Phase III Efficacy PK/PD	Study OM-EPA-004	To evaluate efficacy and safety of adding Epanova to statin therapy for lowering non-HDL cholesterol in subjects with persistent hypertriglyceridemia and high-risk for cardiovascular disease.	Randomized, double-blind, olive oil controlled, parallel group design	Epanova 2g QD (n=215); Epanova 4g QD (n=216) Olive oil (placebo) QD arm (n=216)	647	Subjects at high risk for a future cardiovascular event (with high serum TG ≥200 and < 500 mg/dL despite being on a statin for at least 4 weeks prior to screening	6 weeks
Phase III	Study TP0307 (EPIC-1)	To assess the ability of Epanova Soft Gelatin Capsules taken at a total daily dose of 4 g to maintain remission in Crohn's Disease patients in whom remission, stable for at least 3 months and no longer than 1 year, had been induced by corticosteroids, azathioprine/6-MP, methotrexate, 5-ASA or antibiotics.	Multi-centre, randomized, double-blind, placebocontrolled, parallel-group study.	Epanova: Week 1: 1g, Week 2: 2g (1g BID), Week 3 to Week 52: 4g (2g BID) (n=188) Placebo (TG): Week 1: 1g Week 2: 2g (1g BID), Week 3 to Week 52: 4g (2g BID) (n=186) 52 Weeks	383	Subjects in remission from CD 3- 12 months, (CDAI < 120) and off steroids and immunosuppressants	52 weeks
Phase III	Study TP0308 (EPIC-2)	To assess the efficacy and safety of Epanova for the	Randomized, placebocontrolled, double-blind,	Epanova: 1g for 7 days; 2g (1g BID) days 8-14; 4g	379	Subjects with active Crohn's disease who respond to induction	

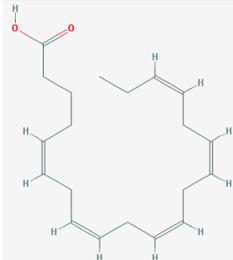
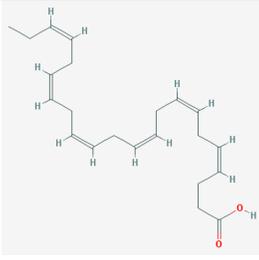
Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
		maintenance of symptomatic remission in subjects with CD who are responding to steroid induction therapy.	parallel group, multicenter study.	(2g BID) daily thereafter (n=189) Placebo (TG): Same regimen (n=190)		therapy and are in remission prior to study therapy period	
Phase IIb	Study TP0309 (EPIC-3)	PK/PD, safety and tolerability of Epanova in CD patients in remission	Two-center open-label, no comparator	Epanova 4g (2g BID)	25	Subjects in remission from Crohn's Disease 3-24 months (CDAI < 150) and off steroids/ immunosuppressants	52 weeks
Phase III	Study TP0307 (EPIC-1E)	To assess the long term safety and tolerability profile of Epanova in patients with CD	Multi-center, open-label, extension study, all subjects received Epanova	1g x 7 days, then 2g (1g BID) on days 8-14 and to 4 g (2g BID)	82	Subjects enrolled to EPIC-1, EPIC-2, or EPIC-3 regardless of treatment received in those studies	36 months

(Source: Epanova NDA eCTD module 5.2; Tables 5.2-1 and 5.2-2, pages 2-7)

2.2 General Attributes

Epanova is a complex drug substance consisting of a mixture of polyunsaturated free fatty acids (PUFAs) derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids. Omega-3 fatty acid treatment is proposed to lower triglyceride (TG) levels by reducing the amount of hepatic TG secretion in VLDL and by enhancing the rate of TG clearance from circulation. Hepatic TG secretion is decreased by gene regulation resulting in reduced hepatic lipogenesis and increased mitochondrial and peroxisomal β -oxidation of fatty acids.

2.2.1 What are the highlights of the Epanova drug product as they relate to clinical pharmacology review?

	Epanova	
	EPA	DHA
Appearance	Colorless to slightly yellow clear oil	Colorless to faint yellow clear oil
Chemical Name (IUPAC)	(5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentenoic acid	(4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoic acid
Molecular Formula	C ₂₀ H ₃₀ O ₂	C ₂₂ H ₃₂ O ₂
Molecular Weight	302.451	328.488
Structural Formula		
Solubility	Soluble in 100% ethanol	Soluble to 100 mM in DMSO
Boiling Point	439.3 °C at 760 mmHg	836.1°F (446.7°C)
Amount contained in each 1g capsule	500 to 600 mg/g	150 to 250 mg/g

2.2.2 What is the composition of to-be-marketed formulation of Epanova?

Formulation: The drug product, Epanova, is a soft gelatin oblong capsule containing 1,000 mg of omega-3 fatty acids sourced from fish oils and coated with a red/brown pigmented polymeric coat. (b) (4) Each Epanova capsule contains not less than 850 mg of polyunsaturated fatty acids. The predominant omega-3 fatty acids are eicosapentaenoic acid (EPA 500-600 mg), docosahexaenoic acid (DHA 150-250 mg) and docosapentaenoic acid (DPA (b) (4) mg). Epanova capsules have an imprinted product identification code in white ink. The container closure system is a commercially available white opaque high density polyethylene bottle with a (b) (4) screw cap. The drug product is packaged in a 150 mL bottle containing 60 capsules. The formulation is shown in [Table 5](#).

Table 5 Phase 3/commercial formulation

Ingredient	Function	Specification	Weight Per Capsule (mg)
Omefas ^a	Active ingredient	3.2.S.4.1	1,000
Capsule Shell			
Gelatin (porcine type A, (b) (4))	Capsule shell	USP/NF, Ph. Eur.	(b) (4)
Sorbitol (b) (4)			
Glycerol (b) (4)			
Purified Water			
Total shell weight			
Capsule Coating			
Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4)	(b) (4)	NF, Ph. Eur., JP	(b) (4)
Talc		USP/NF	
Titanium dioxide		USP/NF	
Iron oxide red		USP/NF	
Polysorbate 80		USP/NF	
Carboxymethylcellulose sodium		USP/NF, Ph. Eur.	
Purified water		USP, Ph. Eur.	
Total coating weight			
Printing Ink ^d	Identification	USP/NF	-
Total capsule weight			1,470.0
a = (b) (4)			
b = (b) (4)			
c = (b) (4)			
d = The qualitative composition of the ink is provided in Table 3.2.P.1-2			
e = (b) (4)			

(Source: Epanova NDA eCTD module 3.2.P.1; Table 3.2.P.1-1, page 3)

2.2.3 What are the proposed mechanism of action and therapeutic indications?

According to the sponsor, mechanistic studies suggest that omega-3 fatty acid treatment lowers the triglyceride (TG) level by both reducing the amount of hepatic TG secretion and by enhancing the rate of TG clearance from circulation (*CSR for study OM-EPA-003, section 13, page 135*). Apolipoprotein C-III (Apo CIII) appears to play an important role in the pathogenesis of hypertriglyceridemia, particularly with regard to inhibiting the actions of lipoprotein lipase and hepatic lipase, which slows TG hydrolysis. Apo CIII also interferes with the interactions of TG-rich lipoproteins with hepatic Apo B/E receptors, slowing the removal of these particles from circulation. Apo CIII is regulated by the hepatic nuclear factor (HNF)-4-alpha, forkhead box protein O1 transcription factor (FOXO1) and carbohydrate response element binding protein (ChREBP) in response to insulin. An increase in Apo CIII synthesis may represent a compensatory mechanism to reduce the catabolism of TG-rich lipoproteins and uptake by hepatic receptors in an attempt to cope with a large influx of substrates for TG production. The effect of omega-3's on Apo CIII, is independent of peroxisome proliferator activated receptor-alpha (PPAR-alpha). Both EPA and DHA down-regulate sterol regulatory element binding protein 1c (SREBP-1c), the transcription factor that controls lipogenesis. EPA is a more potent agonist of PPAR-alpha than DHA, while DHA appears to regulate HNF-4 alpha, FOXO1 and ChREBP. Thus, while both EPA and DHA down-regulate TG synthesis in the liver, the clinical data support the hypothesis that DHA, by regulating different hepatic transcription factors than EPA (i.e.,

FOXO1 and ChREBP), reduces Apo CIII production, resulting in enhanced conversion of VLDL to LDL and the formation of larger more buoyant LDL particles reflected by an increase in the LDL-C/Apo B ratio. The two commercially available fish oil products, Lovaza (containing the ethyl esters of EPA and DHA), and Vascepa (containing the ethyl ester of EPA) are indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Proposed indication for Epanova is as an adjunct to diet to reduce triglyceride (TG), levels in adult patients with severe (>500 mg/dL) hypertriglyceridemia.

2.2.4 What are the proposed dosages and routes of administration?

The (b) (4) daily dose of Epanova is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules). Though the 4 gram dose did not demonstrate any additional benefit over the 2 gram dose, (b) (4) the daily dosage may be (b) (4) taken as a single 4-gram dose (4 capsules).

In addition, the following dosing recommendations are proposed by the sponsor:

- Assess triglyceride levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride levels and manage as appropriate.
- Patients should be placed on an appropriate lipid-lowering diet before receiving Epanova, and should continue this diet during treatment with Epanova. In clinical studies, Epanova was administered without regard to meals.
- Patients should be advised to swallow Epanova capsules whole, and not break open, crush, dissolve or chew Epanova.

Reviewer comment:

This reviewer recommends language for (b) (4)

(b) (4) The recommended language is as follows:

- Recommended daily dose of EPANOVA is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules).
- Maximum daily dose should not exceed 4-grams (4 capsules).

2.3 General Clinical Pharmacology

2.3.1 What are the PK characteristics of Epanova after oral administration and how do they relate to the dose?

2.3.1.1 Single Dose

Single-dose pharmacokinetics of Epanova in healthy subjects are available from 2 studies across a dose range of 2g to 8 g (studies OM-EPA-001, and SPC 275-4). Upon oral administration, maximum concentrations of EPA and DHA in systemic circulation were achieved between 4.5 – 5.5 hours in healthy subjects.

Across these dose groups, the elimination half- life was approximately 7.1 – 15.7 hours for healthy subjects.

Representative mean plasma concentration-time profiles of EPA and DHA following single-dose are illustrated in [Figure 3](#) below for normal healthy volunteers.

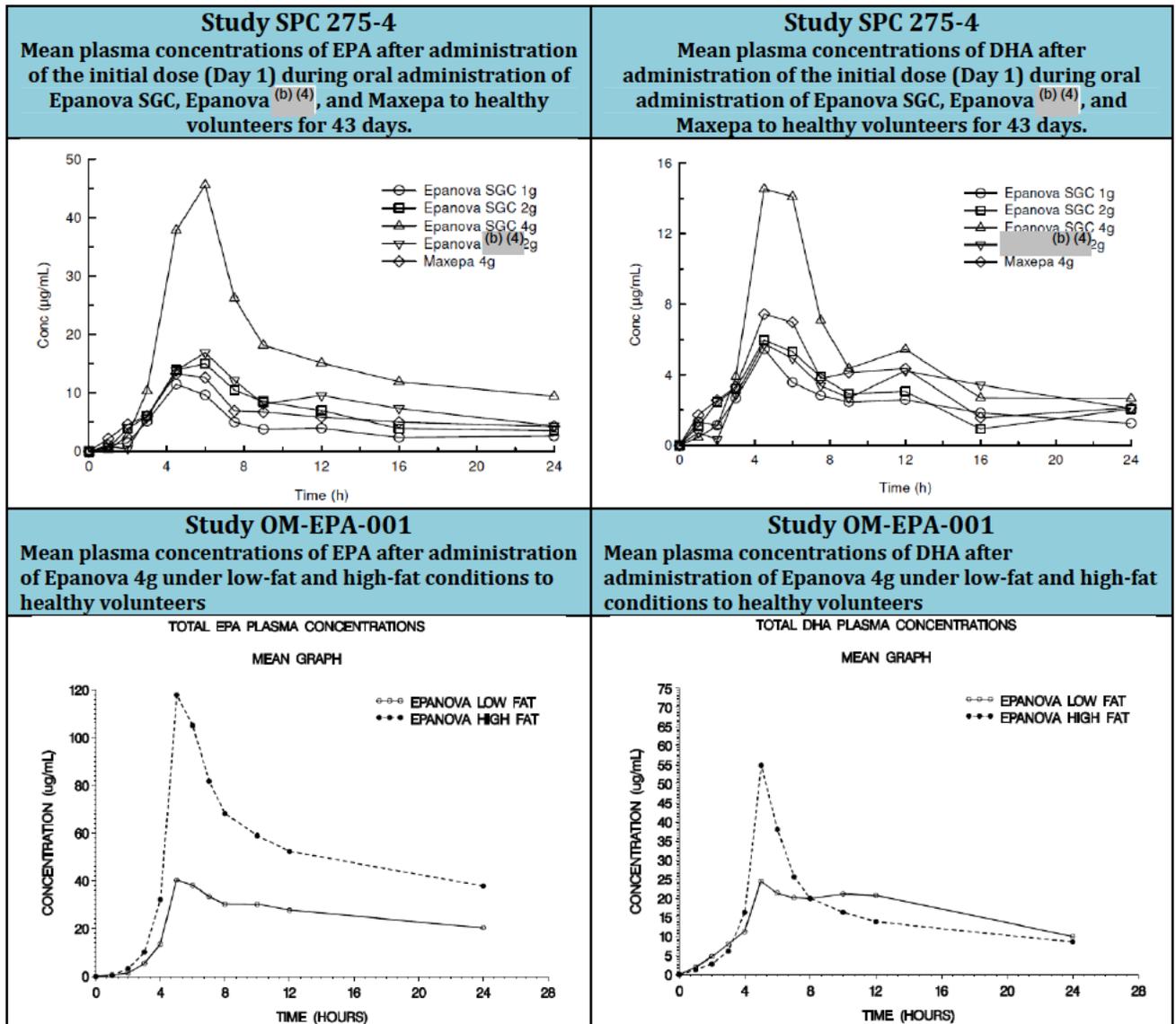


Figure 3 Mean plasma concentration time profile of EPA and DHA oral doses of Epanova

(Source: study SPC275-4, Figure 4, Page 19; Figure 8, Page 24 and Study OM-EPA-001, Figure 14.2.5.3.3, Page 214; Figure 14.2.6.3.3, Page 243)

The mean and SD of pharmacokinetic parameters for EPA and DHA across the single-dose studies are presented in [Tables 6](#) and [7](#) below.

Table 6 Pharmacokinetic parameters of EPA and DHA after single oral doses from 2 g to 8 g in healthy subjects.

EPA

Parameter ¹	Epanova SGC 1 g (2 g/day)	Epanova SGC 2 g (4 g/day)	Epanova SGC 4 g (8 g/day)	Epanova (b) (4) 2 g (4.5 g/day)	Maxepa 4.5 g (9 g/day)
Day 1					
C _{max} (µg/mL)	14.5 ± 7.98	20.5 ± 8.16	54.3 ± 28.5	24.4 ± 13.5	16.1 ± 5.47
T _{max} (h)	4.50	5.32	5.46	6.02	4.72
AUC _{0-t} (h•µg/mL)	85.9 ± 39.2	153 ± 56.0	356 ± 182	178 ± 74.3	130 ± 61.8
AUC _∞ (h•µg/mL)	143; 161	— ²	681 ± 295	199	— ²
t _{1/2} (h)	8.25; 10.5	— ²	15.7 ± 2.98	7.19	— ²

DHA

Parameter ¹	Epanova SGC 1 g (2 g/day)	Epanova SGC 2 g (4 g/day)	Epanova SGC 4 g (8 g/day)	Epanova (b) (4) 2 g (4.5 g/day)	Maxepa 4.5 g (9 g/day)
Day 1					
C _{max} (µg/mL)	6.88 ± 4.80	7.80 ± 2.93	19.4 ± 9.83	8.65 ± 4.66	9.79 ± 3.46
T _{max} (h)	5.26	5.32	4.73	9.02	4.51
AUC _{0-t} (h•µg/mL)	44.5 ± 27.1	61.8 ± 28.0	97.2 ± 54.1	64.6 ± 37.6	61.8 ± 38.4
AUC _∞ (h•µg/mL)	— ²	— ²	— ²	92.1	— ²
t _{1/2} (h)	— ²	— ²	— ²	2.63	— ²

(source: Report of Study 275-4; Table 7, Page 21 and Table 9, page 25)

Table 7 Pharmacokinetic parameters of EPA and DHA after single oral dose of 4 g under low-fat and high-fat conditions in healthy volunteers.

EPA

TREATMENT	N Obs	Variable	N	Minimum	Maximum	Median	Mean	Std Dev	Coeff of Variation
A:TEST	51	AUCT	51	262.3415	1770.4283	811.2568	901.7743	396.5603	43.9756
		C _{MAX}	51	13.2500	180.0000	55.6500	64.1482	38.1149	59.4169
		T _{MAX}	51	5.0000	24.0000	6.0000	7.9846	4.6143	57.7900
		LNAUCT	51	5.5696	7.4790	6.6986	6.7093	0.4465	6.6550
		LNC _{MAX}	51	2.5840	5.1930	4.0191	3.9944	0.5927	14.8384
TREATMENT	N Obs	Variable	N	Minimum	Maximum	Median	Mean	Std Dev	Coeff of Variation
B:REFERENCE	51	AUCT	51	650.4687	2991.9483	1462.8950	1550.4515	519.1053	33.4809
		C _{MAX}	51	41.1600	343.6000	138.2000	149.1306	65.4121	43.8623
		T _{MAX}	51	4.0000	12.0000	5.0000	5.9807	1.9132	31.9893
		LNAUCT	51	6.4777	8.0037	7.2882	7.2963	0.3157	4.3263
		LNC _{MAX}	51	3.7175	5.8395	4.9287	4.9079	0.4583	9.3371

DHA

TREATMENT	N Obs	Variable	N	Minimum	Maximum	Median	Mean	Std Dev	Coeff of Variation
A:TEST	51	AUCT	51	706.8391	2999.1167	1669.2617	1762.7166	518.3161	29.4044
		C _{MAX}	51	34.6600	181.7000	88.4100	92.1769	29.9953	32.5411
		T _{MAX}	51	5.0000	24.0000	7.0000	8.5768	4.2089	49.0727
		LNAUCT	51	6.5608	8.0061	7.4201	7.4319	0.2982	4.0120
		LNC _{MAX}	51	3.5456	5.2024	4.4820	4.4720	0.3278	7.3309
TREATMENT	N Obs	Variable	N	Minimum	Maximum	Median	Mean	Std Dev	Coeff of Variation
B:REFERENCE	51	AUCT	51	738.2458	3380.5567	1760.3267	1864.1878	549.2311	29.4622
		C _{MAX}	51	48.1700	234.5000	120.9000	122.9400	39.4245	32.0681
		T _{MAX}	51	3.0000	24.0000	5.0000	5.7075	2.9951	52.4770
		LNAUCT	51	6.6043	8.1258	7.4733	7.4901	0.2875	3.8390
		LNC _{MAX}	51	3.8747	5.4575	4.7950	4.7583	0.3394	7.1339

(source: Study Report OM-EPA-001; Table 14.2.11.3.1, page 384-385, and Table 14.2.12.3.1, page 413-414)

2.3.1.2 Multiple Once Daily Doses

Multiple-dose pharmacokinetics of EPA and DHA in healthy subjects are available from 2 multiple dose studies across a dose range of 2 g QD to 8 g QD (OM-EPA-006 and SPC 275-4). Multiple dose data for the plasma PK of Epanova in hyper triglyceridemic patients are available from 2 studies across a dose range of 2 g QD to 4 g QD (OM-EPA-003 and OM-EPA-004). In another multiple-dose study (OM-EPA-007), only trough levels were collected for EPA and DHA at baseline and Day 15. Baseline corrected data are available for all studies.

Representative mean plasma concentration-time profiles of EPA and DHA following multiple-dose are illustrated in [Figure 4](#) below.

After multiple dose administration, the extent of absorption was dose proportional in healthy subjects between dose levels of 2 and 8 g QD. In study SPC 275-4, mean plasma concentrations of EPA increased in a dose-proportional manner after administration of the initial (day 1, single-dose) and final (day 43, steady-state) doses of Epanova at doses of 1g (2 g/day), 2g (4 g/day), and 4g (8 g/day), as did mean values for C_{max} and AUC_{0-t} (single-dose) or AUC₀₋₁₂ (steady-state) ([Table 8](#)). Relationship between EPA and DHA C_{max} and AUC following single-dose and at steady-state are shown in [Figure 5](#).

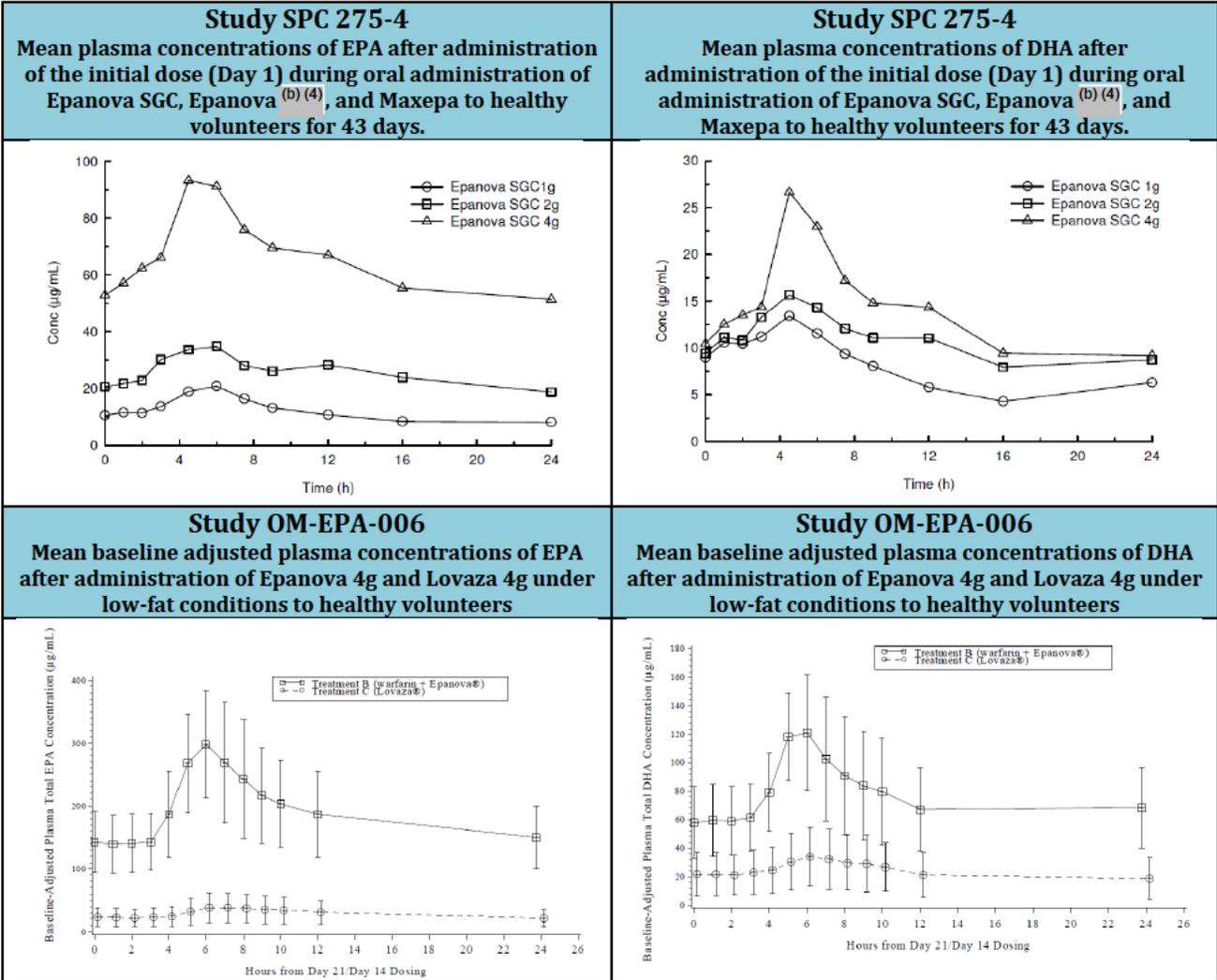


Figure 4 Mean plasma concentration time profile of EPA and DHA after multiple oral doses of 2 g - 8 g

(Source: Study SPC 275-4, Figure 5, Page 20; Study SPC 275-4, Figure 9, Page 24; Study OM-EPA-006, Figure 9, Page 55; Study OM-EPA-006, Figure 13, Page 60)

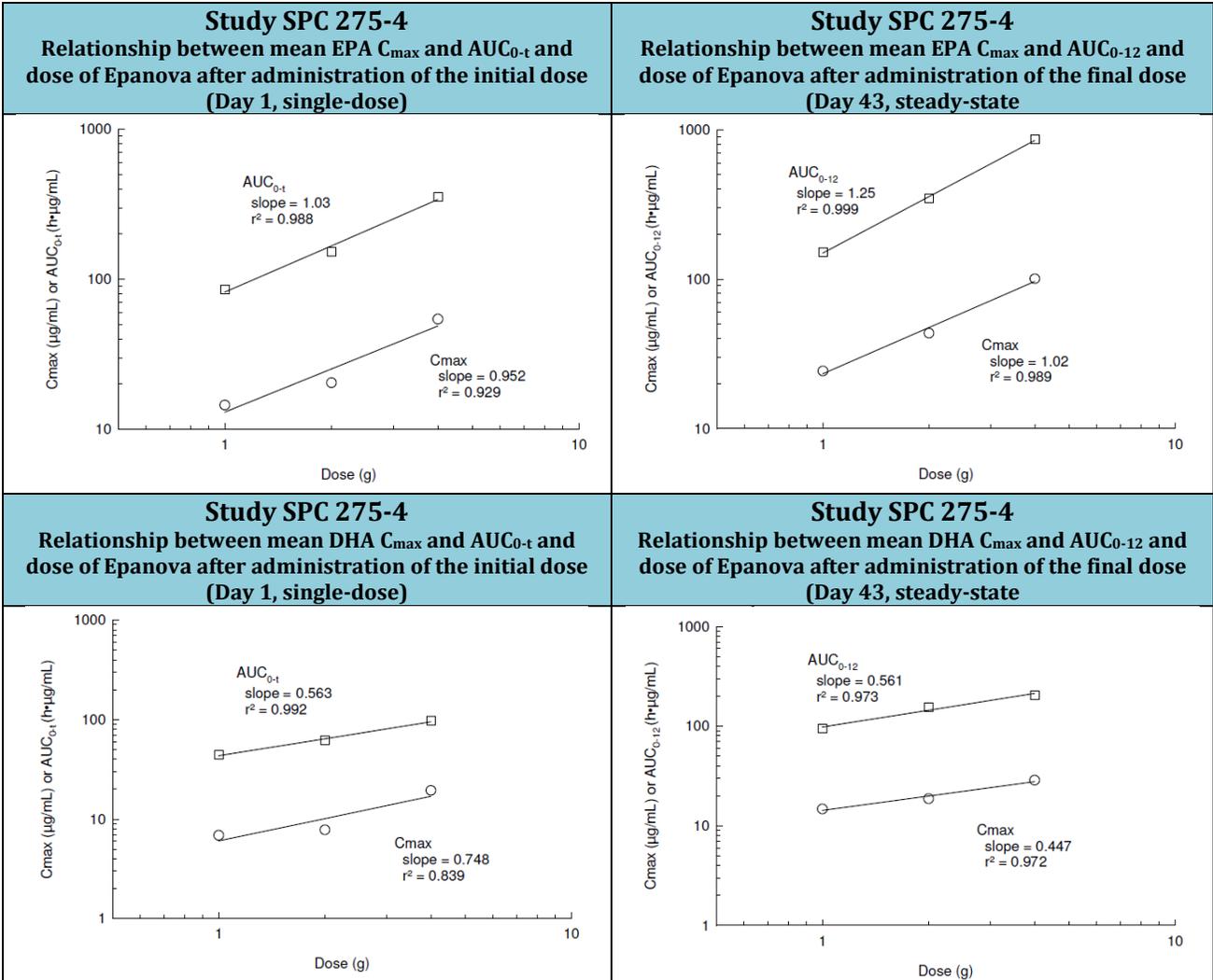


Figure 5 Relationship between Dose and PK Parameters, C_{max} and AUC for EPA and DHA

(Source: Study SPC 275-4, Figure 6, Page 22; Study SPC 275-4, Figure 7, Page 22; Study SPC 275-4, Figure 10, Page 26, Study SPC 275-4, Figure 11, Page 26)

The mean and SD of pharmacokinetic parameters for EPA and DHA across the multiple-dose studies in healthy subjects are presented in [Table 9](#) below.

Table 8 Pharmacokinetic parameters of EPA and DHA after multiple oral doses from 2 g to 8 g in healthy subjects from Study SPC 275-4.

EPA

Parameter ¹	Epanova SGC 1 g (2 g/day)	Epanova SGC 2 g (4 g/day)	Epanova SGC 4 g (8 g/day)	Epanova (b) (4) 2 g (4.5 g/day)	Maxepa 4.5 g (9 g/day)
Day 43					
C _{max} (µg/mL)	24.3 ± 11.0	43.5 ± 15.9	101 ± 44.3	— ³	— ³
T _{max} (h)	5.25	4.50	4.50	— ³	— ³
AUC ₀₋₁ (h•µg/mL)	165.5 ± 74.7	330 ± 131	854 ± 385	— ³	— ³
AUC ₀₋₁₂ (h•µg/mL)	151 ± 49.0	345 ± 126	859 ± 403	— ³	— ³
t _{1/2} (h)	18.7	18.1	21.9 ± 12.9	— ³	— ³

¹Mean ± standard deviation except for T_{max} for which the median is reported. If N ≤ 2, then the individual values are reported.

³Due to an administrative change, plasma concentrations were not measured on Day 43 for this treatment.

DHA

Parameter ¹	Epanova SGC 1 g (2 g/day)	Epanova SGC 2 g (4 g/day)	Epanova SGC 4 g (8 g/day)	Epanova (b) (4) 2 g (4.5 g/day)	Maxepa 4.5 g (9 g/day)
Day 43					
C _{max} (µg/mL)	14.8 ± 11.0	18.7 ± 8.48	28.7 ± 16.9	— ³	— ³
T _{max} (h)	4.50	4.50	4.50	— ³	— ³
AUC ₀₋₁ (h•µg/mL)	113 ± 80.4	144 ± 77.0	202 ± 126	— ³	— ³
AUC ₀₋₁₂ (h•µg/mL)	94.6 ± 40.6	156 ± 78.6	206 ± 131	— ³	— ³
t _{1/2} (h)	— ²	— ²	13.5; 2.44	— ³	— ³

¹Mean ± standard deviation except for T_{max} for which the median is reported. If N ≤ 2, then the individual values are reported.

²Parameter could not be calculated for any subjects for this treatment.

³Due to an administrative change, plasma concentrations were not measured on Day 43 for this treatment.

(source: Study 275-4; Table 7, page 21, and Table 9, page 25)

Table 9 Pharmacokinetic parameters of EPA and DHA after multiple oral dose of 4 g in healthy subjects from Study OM-EPA-006

EPA

Pharmacokinetic Parameters	Treatment B (n = 25)^a	Treatment C (n = 26)^b
C _{max,ss} (µg/mL)	295.0 (30.44)	34.22 (66.87)
t _{max,ss} (hr)	6.00 (5.00, 8.00)	6.56 (5.00, 9.00)
C _{min,ss} (µg/mL)	126.1 (31.81)	17.01 (66.23)
C _{avg,ss} (µg/mL)	178 (33.4)	24.0 (65.7)
Flux (%)	96.2 (24.8)	71.9 (28.3)
Swing (%)	137 (29.1)	105 (40.7)
AUC _(0-tau) (µg*hr/mL)	4230 (33.4)	576 (65.7)
t _½ (hr)	36.7 (46.1)	22.8 (33.3)
k _{el} (1/hr)	0.0221 (36.8)	0.0344 (38.7)
CL/F (mL/hr)	548 (32.4)	3570 (77.8)
^a n=19 for t _½ and k _{el} . ^b n=24 for t _½ and k _{el} . t _{max,ss} is presented as Median (Minimum, Maximum). C _{max,ss} , C _{min,ss} , C _{avg,ss} and AUC _(0-tau) are presented as Geometric Mean (Geometric CV%). Flux, Swing, t _½ , k _{el} , and CL/F are presented as Arithmetic Mean (Arithmetic CV%). Treatment B: A 4 g dose of Epanova [®] on Days 8 - 28 (fed), co-administered with a single 25 mg dose of warfarin on Day 22 (fasted). Treatment C: A 4 g dose of Lovaza [®] on Days 1 - 14 (fed). Source: Tables 14.2.1.5.3 through 14.2.1.5.4		

DHA

Pharmacokinetic Parameters	Treatment B (n = 25) ^a	Treatment C (n = 26) ^b
C _{max,ss} (µg/mL)	124.1 (29.84)	30.56 (68.30)
t _{max,ss} (hr)	6.00 (5.00, 9.00)	6.03 (5.00, 12.0)
C _{min,ss} (µg/mL)	50.88 (47.60)	15.00 (85.35)
C _{avg,ss} (µg/mL)	69.9 (41.0)	22.4 (60.5)
Flux (%)	108 (40.7)	89.5 (38.2)
Swing (%)	154 (54.2)	154 (79.8)
AUC _(0-t) (µg*hr/mL)	1660 (41.0)	412 (114)
AUC _(0-tau) (µg*hr/mL)	1660 (41.0)	537 (60.5)
t _½ (hr)	46.2 (53.6)	18.2 (67.1)
k _{el} (1/hr)	0.0178 (39.3)	0.0897 (142)
CL/F (mL/hr)	518 (38.7)	2970 (55.2)

^a n=6 for t_½ and k_{el}.
^b n=23 for C_{min,ss}, C_{avg,ss}, Flux, Swing, AUC_(0-tau), and CL/F; n=11 for t_½ and k_{el}.
t_{max,ss} is presented as Median (Minimum, Maximum).
C_{max,ss}, C_{min,ss}, C_{avg,ss}, AUC_(0-t) and AUC_(0-tau) are presented as Geometric Mean (Geometric CV%).
Flux, Swing, t_½, k_{el}, and CL/F are presented as Arithmetic Mean (Arithmetic CV%).
Treatment B: A 4 g dose of Epanova[®] on Days 8 - 28 (fed), co-administered with a single 25 mg dose of warfarin on Day 22 (fasted).
Treatment C: A 4 g dose of Lovaza[®] on Days 1 - 14 (fed).

Source: [Tables 14.2.1.7.3](#) through [14.2.1.7.4](#)

(source: Study OM-EPA-006; Table 14, Page 72 and Table 18, page 76)

Reviewer Comments:

Several factors such as (a) different assays used in the program for estimation of EPA and DHA – GC assay for Study SPC275-4, (b) LC-MS/MS assay for studies 001 and 006, (c) CLIA based diagnostic assay for study 007, make it difficult to pool the data or make a valid comparison of the data across studies. In addition, the dietary information for SPC275-4 is unknown.

2.3.2 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

The pharmacokinetics of EPA were linear after administration of single or multiple doses of Epanova SGC at doses of 2, 4, and 8 g/day. There was an approximate 2-fold accumulation of EPA during continued dosing.

Mean plasma concentrations and pharmacokinetic parameters for DHA increased in a less than dose-proportional manner after administration of single or multiple doses of Epanova SGC at doses of 2, 4, and 8 g/day. There was an approximate 2- to 3-fold accumulation of DHA during continued dosing.

Representative plot and data for EPA are shown in [Figure 6](#) and [Table 10](#), respectively. The relationship between EPA C_{max} , AUC and dose is shown in [Figure 7](#).

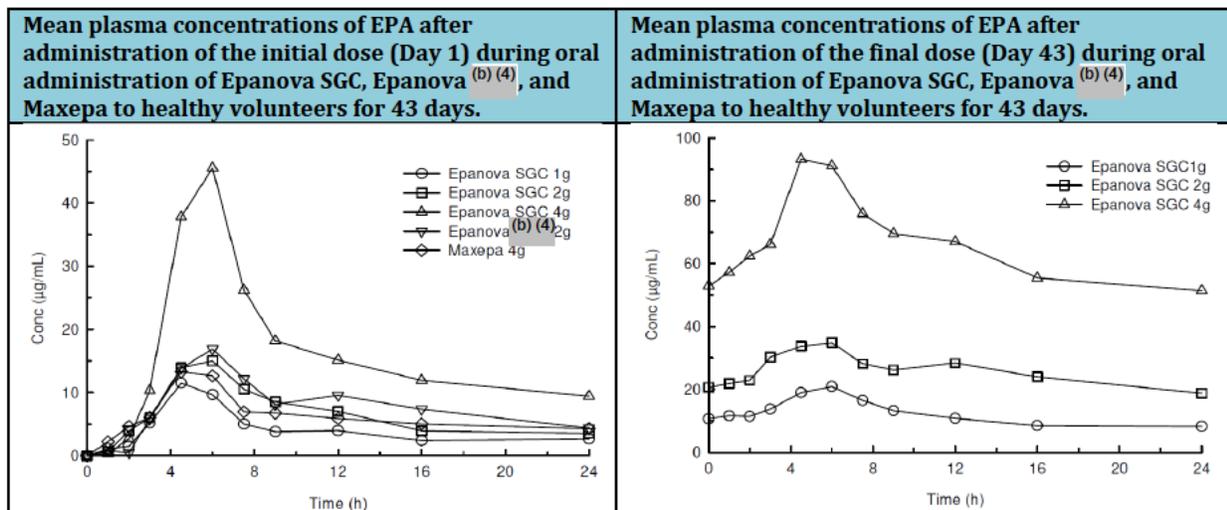


Figure 6 Mean plasma concentration time profile of EPA after single and multiple doses of Epanova soft gelatin capsules 1, 2 and 4 g, Epanova ^{(b) (4)} capsules 2 g and a comparator Maxepa 4g

(source: sponsor's study SPC 275-4; Figure 4, page 19 and Figure 5, Page 20)

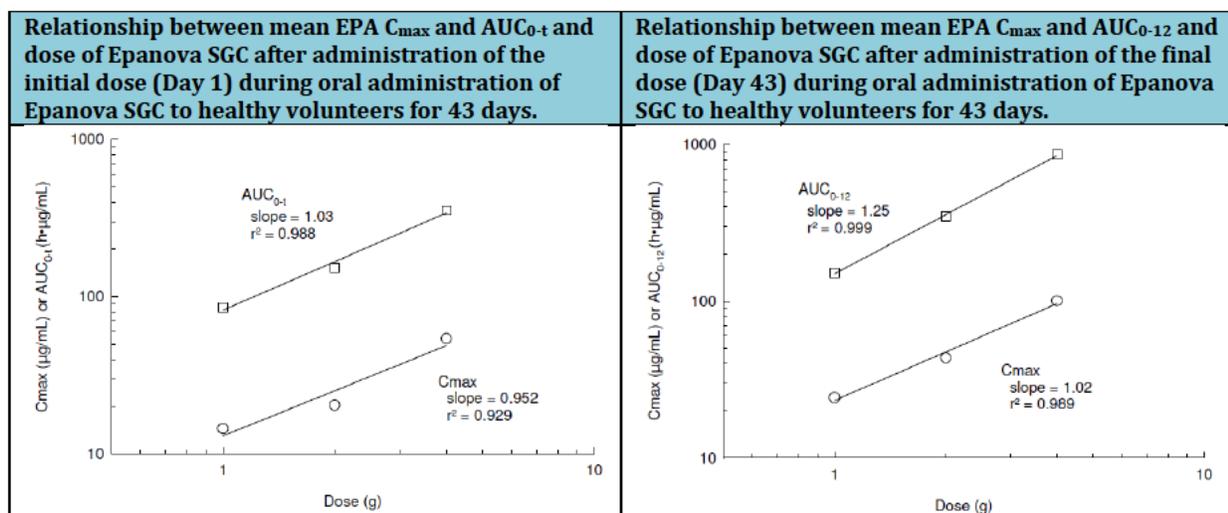


Figure 7 Relationship between mean EPA C_{max} and AUC₀₋₁₂ and dose of Epanova SGC following single and multiple dose

(source: sponsor's study SPC 275-4; Figures 6 and 7, page 22)

Table 10 Pharmacokinetic parameters for EPA after administration of SGC, Epanova ^{(b) (4)}, and Maxepa to healthy volunteers for 43 days.

Parameter ¹	Epanova SGC 1 g (2 g/day)	Epanova SGC 2 g (4 g/day)	Epanova SGC 4 g (8 g/day)	Epanova ^{(b) (4)} 2 g (4.5 g/day)	Maxepa 4.5 g (9 g/day)
Day 1					
C _{max} (µg/mL)	14.5 ± 7.98	20.5 ± 8.16	54.3 ± 28.5	24.4 ± 13.5	16.1 ± 5.47
T _{max} (h)	4.50	5.32	5.46	6.02	4.72
AUC _{0-t} (h·µg/mL)	85.9 ± 39.2	153 ± 56.0	356 ± 182	178 ± 74.3	130 ± 61.8
AUC _∞ (h·µg/mL)	143; 161	— ²	681 ± 295	199	— ²
t _{1/2} (h)	8.25; 10.5	— ²	15.7 ± 2.98	7.19	— ²
Day 43					
C _{max} (µg/mL)	24.3 ± 11.0	43.5 ± 15.9	101 ± 44.3	— ³	— ³
T _{max} (h)	5.25	4.50	4.50	— ³	— ³
AUC _{0-t} (h·µg/mL)	165.5 ± 74.7	330 ± 131	854 ± 385	— ³	— ³
AUC ₀₋₁₂ (h·µg/mL)	151 ± 49.0	345 ± 126	859 ± 403	— ³	— ³
t _{1/2} (h)	18.7	18.1	21.9 ± 12.9	— ³	— ³

¹Mean ± standard deviation except for T_{max} for which the median is reported. If N ≤ 2, then the individual values are reported.

²Parameter could not be calculated for any subjects for this treatment.

³Due to an administrative change, plasma concentrations were not measured on Day 43 for this treatment.

(source: sponsor's study SPC 275-4; Table 7, page 21)

Representative plot and data for DHA are shown in [Figure 8](#) and [Table 11](#), respectively. The relationship between DHA C_{max}, AUC and dose is shown in [Figure 9](#).

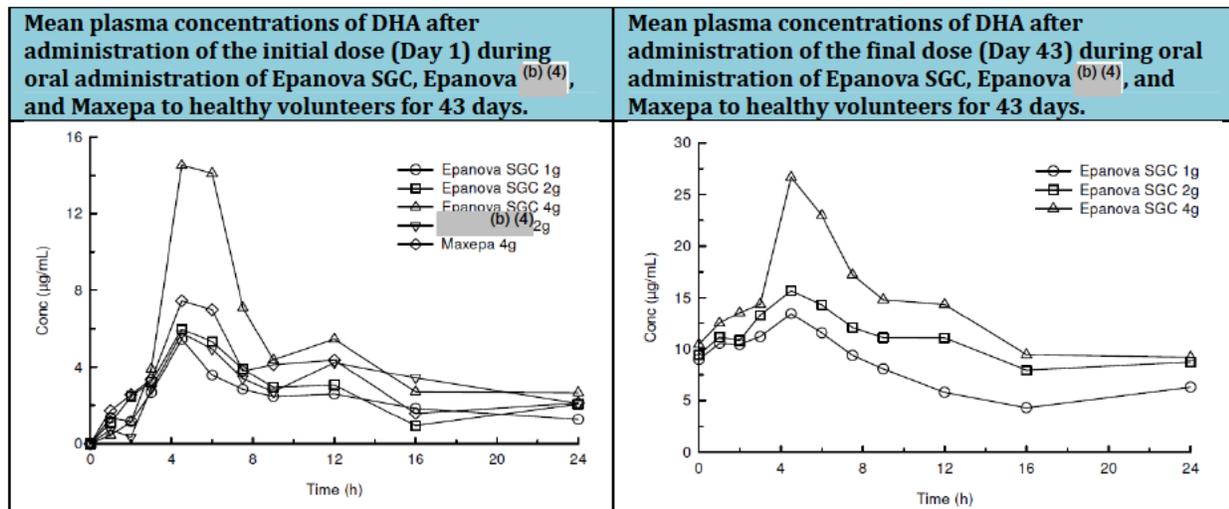


Figure 8 Mean plasma concentration time profile of DHA after single and multiple doses of Epanova soft gelatin capsules 1, 2 and 4 g, Epanova (b) (4) capsules 2 g and a comparator Maxepa 4g

(source: sponsor's study SPC 275-4; Figures 8 & 9, page 24)

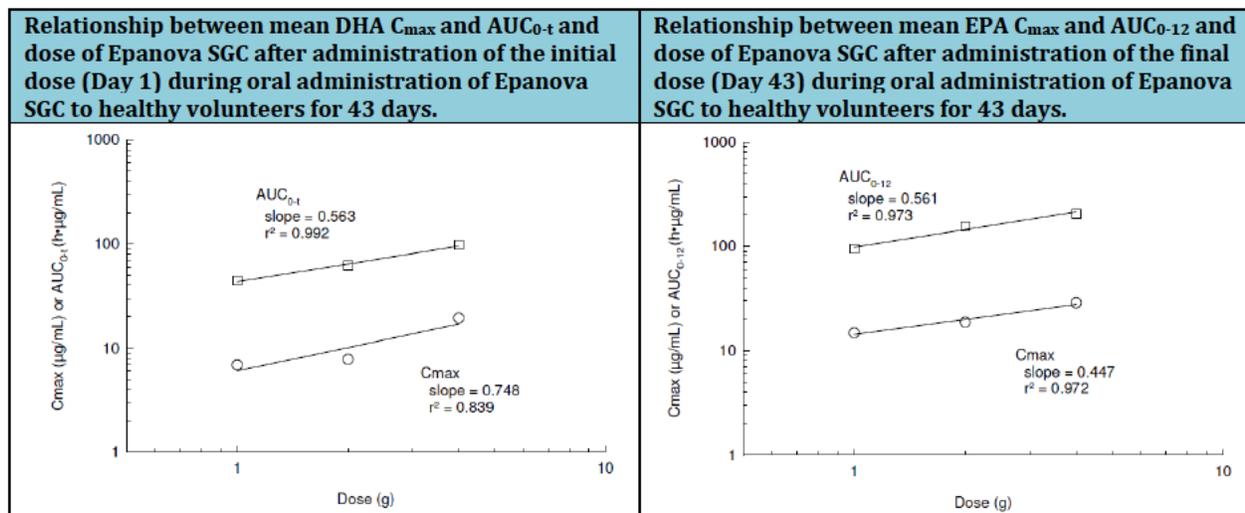


Figure 9 Relationship between mean DHA C_{max} and AUC_{0-12} and dose of Epanova SGC following single and multiple dose

(source: sponsor's study SPC 275-4; Figures 10 and 11, page 26)

Table 11 Pharmacokinetic parameters for DHA after administration of SGC, Epanova ^{(b) (4)}, and Maxepa to healthy volunteers for 43 days.

Parameter ¹	Epanova SGC 1 g (2 g/day)	Epanova SGC 2 g (4 g/day)	Epanova SGC 4 g (8 g/day)	Epanova ^{(b) (4)} 2 g (4.5 g/day)	Maxepa 4.5 g (9 g/day)
Day 1					
C _{max} (µg/mL)	6.88 ± 4.80	7.80 ± 2.93	19.4 ± 9.83	8.65 ± 4.66	9.79 ± 3.46
T _{max} (h)	5.26	5.32	4.73	9.02	4.51
AUC ₀₋₄ (h•µg/mL)	44.5 ± 27.1	61.8 ± 28.0	97.2 ± 54.1	64.6 ± 37.6	61.8 ± 38.4
AUC _∞ (h•µg/mL)	— ²	— ²	— ²	92.1	— ²
t _{1/2} (h)	— ²	— ²	— ²	2.63	— ²
Day 43					
C _{max} (µg/mL)	14.8 ± 11.0	18.7 ± 8.48	28.7 ± 16.9	— ³	— ³
T _{max} (h)	4.50	4.50	4.50	— ³	— ³
AUC ₀₋₄ (h•µg/mL)	113 ± 80.4	144 ± 77.0	202 ± 126	— ³	— ³
AUC ₀₋₁₂ (h•µg/mL)	94.6 ± 40.6	156 ± 78.6	206 ± 131	— ³	— ³
t _{1/2} (h)	— ²	— ²	13.5; 2.44	— ³	— ³

¹Mean ± standard deviation except for T_{max} for which the median is reported. If N ≤ 2, then the individual values are reported.

²Parameter could not be calculated for any subjects for this treatment.

³Due to an administrative change, plasma concentrations were not measured on Day 43 for this treatment.

(source: sponsor's study SPC 275-4; Table 9, page 25)

Reviewer's Comments:

The pharmacokinetics of EPA were linear after administration of single or multiple doses of Epanova SGC at doses of 2, 4, and 8 g/day. There was an approximate 2-fold accumulation of EPA during continued dosing.

Mean plasma concentrations and pharmacokinetic parameters for DHA, however, increased in a less than dose-proportional manner after administration of single or multiple doses of Epanova SGC at doses of 2, 4, and 8 g/day. This was associated with an approximate 2- to 3-fold accumulation of DHA during continued dosing.

However, as is seen in later sections, this level of accumulation is not of safety concern, and may not be clinically significant.

2.3.3 What are the triglyceride lowering effect of EPA and DHA following Epanova administration and how do they relate to the dose?

The sponsor evaluated the efficacy and safety of Epanova in 399 subjects with severe hypertriglyceridemia (triglyceride levels ≥500 and <2000 mg/dL). The primary efficacy analyses evaluated the effects of each of 3 doses, 2, 3 and 4 g/day of Epanova relative to olive oil on fasting serum TG levels after 12 weeks of treatment. The primary efficacy endpoint for each arm was the percent change in TG levels from baseline (average of Weeks -2, -1 and 0) to the end of treatment (average of Weeks 10 and 12). This prospective, double-blind, randomized, parallel 4-arm study was planned for 12 weeks of treatment and 8 clinic visits: one screening, two washout/diet lead-in, one randomization, and four treatments. The study flow diagram is shown in [Figure 10](#) below:

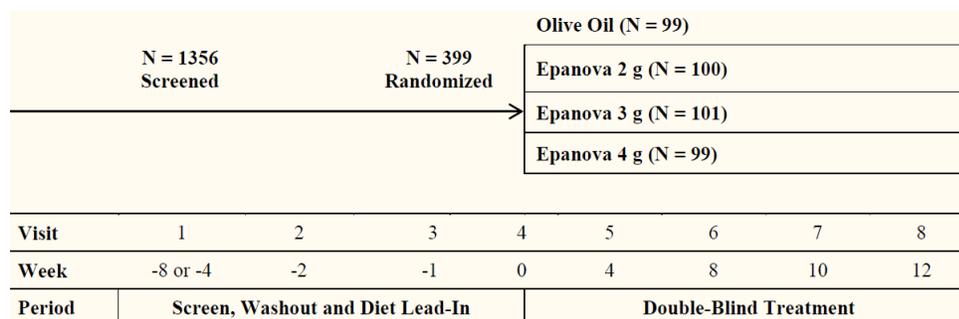


Figure 10 Study Flow Diagram

Percent change in TG levels from baseline to the end of treatment

The primary analysis variable in this trial was the percent change in TG levels from baseline (average of Weeks -2, -1 and 0) to the end of treatment (average of Weeks 10 and 12). The change compared to baseline was evaluated, as summarized in [Table 12](#) below.

Table 12 Baseline and % Change from Baseline to End of Treatment in Serum Triglycerides – MITT and MPP Populations

Triglycerides	Olive Oil (N=99)	Epanova		
		2 g (N=100)	3 g (N=101)	4 g (N=99)
MITT Population				
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]
MPP Population				
Baseline (mg/dL) [1]				
N	92	92	87	90
Mean (SD)	777.0 (299.22)	798.8 (265.60)	796.0 (300.44)	783.1 (329.99)
Median	658.2	736.2	715.0	668.3
Min, Max	417.7, 2006.5	415.3, 1577.8	438.7, 1761.0	435.3, 2094.7
% Change from Baseline [2]				
N	89	92	87	90
Mean (SD)	7.0 (66.34)	-20.9 (35.41)	-16.2 (67.66)	-24.4 (35.18)
Median	-9.6	-25.8	-24.3	-30.5
Min, Max	-76.6, 346.6	-88.5, 150.5	-84.0, 520.1	-78.5, 105.0
LSM [3]	-5.26	-26.55	-26.23	-30.44
95% CI	(-14.38, 4.83)	(-33.48, -18.90)	(-33.37, -18.32)	(-37.07, -23.11)
LSM Difference from Olive Oil		-21.29	-20.97	-25.18
95% CI Bonferroni-corrected		(-40.80, -2.11)	(-40.73, -1.49)	(-44.35, -6.36)
P-value [4]		0.004 [r]	0.004 [r]	< 0.001 [r]

Source: Tables 14.2.1.1 and 14.2.1.2; Listing 16.2.6.1.

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

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

[3] LSM 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: sponsor's study OM-EPA-003; Table 11.4.1, page 62 of 150)

According to the sponsor, the primary endpoint analyses for both the MITT and MPP populations showed clinically meaningful TG lowering from baseline in all three Epanova dose groups. Relative to the olive oil group, the percent TG reductions in each of the Epanova groups were significant.

A plot of percent difference in triglyceride levels from baseline to end of treatment is shown in [Figure 11](#), below for the 3 treatment groups and placebo. The change in % TG lowering from baseline was similar for all three treatment groups, 2 g, 3 g and 4 g. Percent TG lowering from baseline to end of treatment was similar for placebo and the 3 g treatment group. Only the 2 g and 4 g treatment groups were different than placebo.

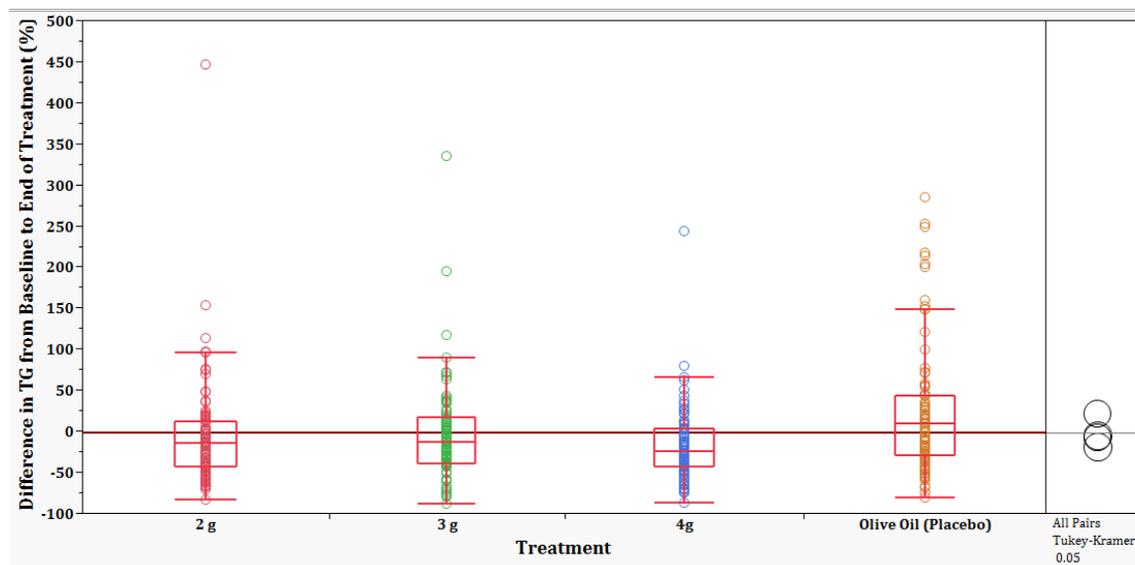


Figure 11 Percent change in Triglyceride Level from Baseline to End of Treatment Following Epanova 2g, 3g, 4g or Placebo (Olive Oil)

Lowering of TG levels (as percent difference from baseline to end of treatment) was evaluated as a function of the increase in EPA or DHA levels (as percent difference from baseline to end of treatment). There were no correlations between lowering of TG levels or increase of EPA or DHA levels ([Figures 12](#) and [13](#)).

There are several limitations to conducting exposure-response relationships when there are at least two active moieties EPA and DHA likely contributing towards efficacy, for the following reasons:

- both of them are also present endogenously
- there is endogenous conversion of EPA to DHA

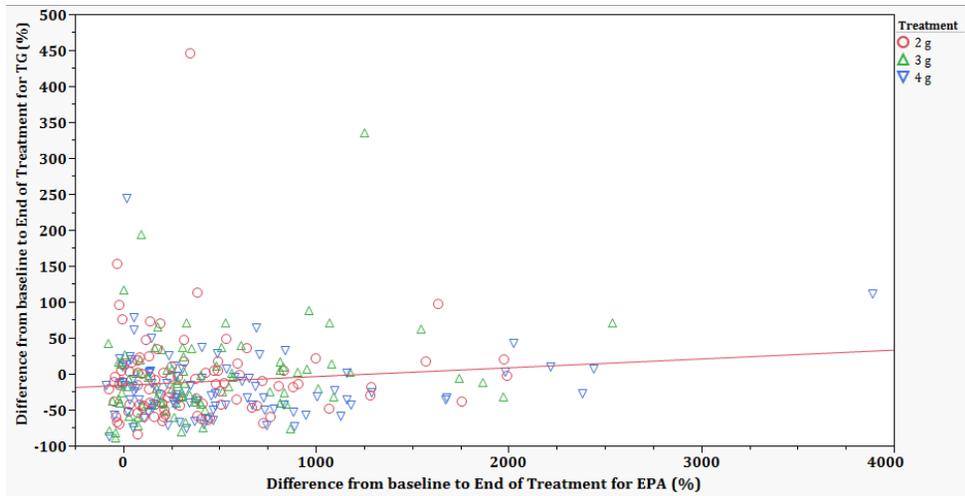


Figure 12 Percent change in Triglyceride Level from Baseline to End of Treatment vs. Percent change in EPA Level from Baseline to End of Treatment Following Epanova 2g, 3g, and 4g

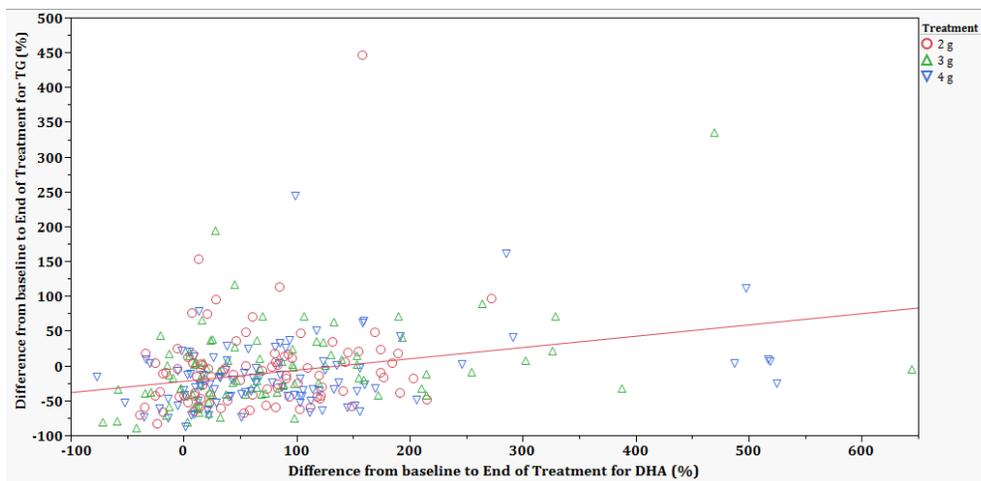


Figure 13 Percent change in Triglyceride Level from Baseline to End of Treatment vs. Percent change in DHA Level from Baseline to End of Treatment Following Epanova 2g, 3g, and 4g

In Study SPC275-4, it was found that the administration of Epanova resulted in dose-related decreases in erythrocyte membrane concentrations of arachidonic acid (AA). An examination of the difference in AA (as percent difference from baseline to end of treatment) as a function of increase in EPA or DHA levels (as percent difference from baseline to end of treatment) showed no correlation in study OM-EPA-003 ([Figures 14](#) and [15](#)).

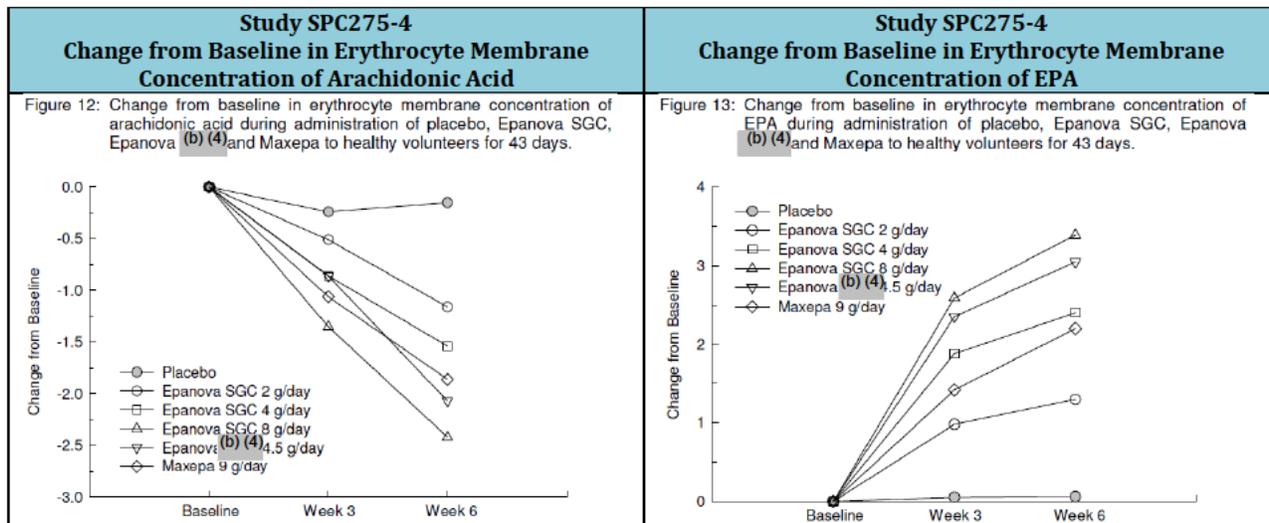


Figure 14 Change from Baseline in Erythrocyte Membrane Concentration of Arachidonic Acid and EPA Following Epanova SGC, Epanova (b) (4) and Maxepa

(source: sponsor's study SPC 275-4; Figures 12 and 13, pages 27 and 28)

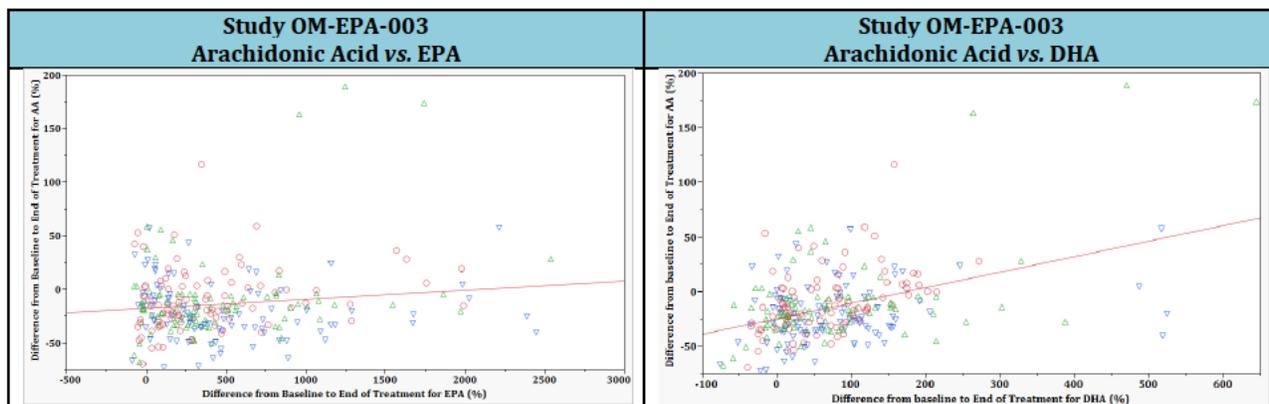


Figure 15 Percent change in Arachidonic Acid Level from Baseline to End of Treatment vs. Percent change in EPA and DHA Level from Baseline to End of Treatment Following Epanova 2g, 3g, and 4g

2.3.4 Is major route of elimination in humans identified?

No mass balance study was conducted with Epanova. EPA is mainly metabolized by the liver via β -oxidation similar to dietary fatty acids. β -oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450 enzymes are also involved in the metabolism, to a lesser extent.

2.3.5 Does this drug prolong the QT or QTc Interval?

As agreed with the Agency in a letter dated October 3, 2012, ECGs collected during the OM-EPA-003 trial were evaluated in lieu of a thorough QTc study.

The ECG data showed no clinically relevant signal of any changes in heart rate, AV conduction as measured by the PR interval duration, cardiac depolarization as measured by the QRS interval duration or new rhythms. It cannot be excluded that omefas was associated with some nonspecific ST changes seen in this trial.

The data from the central tendency comparing the baseline to the single ECG at week 12 on treatment or early termination demonstrated no clear signal of any effect on cardiac repolarization nor did the specific outlier analysis.

According to the sponsor, this study in the target population for Epanova demonstrated no clinically important effects on the ECG and showed no signal of any effect on cardiac repolarization.

2.4 Intrinsic Factors

2.4.1 *What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?*

Information on the pharmacokinetics of EPA and DHA were available from several studies. However, in trial SPC 275-4, EPA and DHA were measured in the triglyceride fraction of human plasma using a GC assay. In study OM-EPA-001, free EPA, free DHA as well as Total EPA and Total DHA were measured (defined as free fatty acid, triglyceride and phospholipids). Study OM-EPA-007 used a CLIA based diagnostic assay to measure trough EPA and DHA levels. Consequently, only data from studies OM-EPA-001 and OM-EPA-006, which used the LC/MS/MS assay, could be pooled. Based on pooled PK analysis age, gender, race and body weight have no clinically meaningful effect on pharmacokinetics of EPA or DHA.

2.4.1.1 Age

Data from Studies OM-EPA-001 and OM-EPA-006 were pooled to examine the effect of intrinsic factors on the apparent oral clearance of EPA. Apparent clearance of EPA was independent of age ([Figure 16](#), and [Figure 17](#), respectively). Apparent clearance was similar for age groups <65 years and ≥65 years of age ([Figure 18](#) for EPA and [Figure 19](#) for DHA).

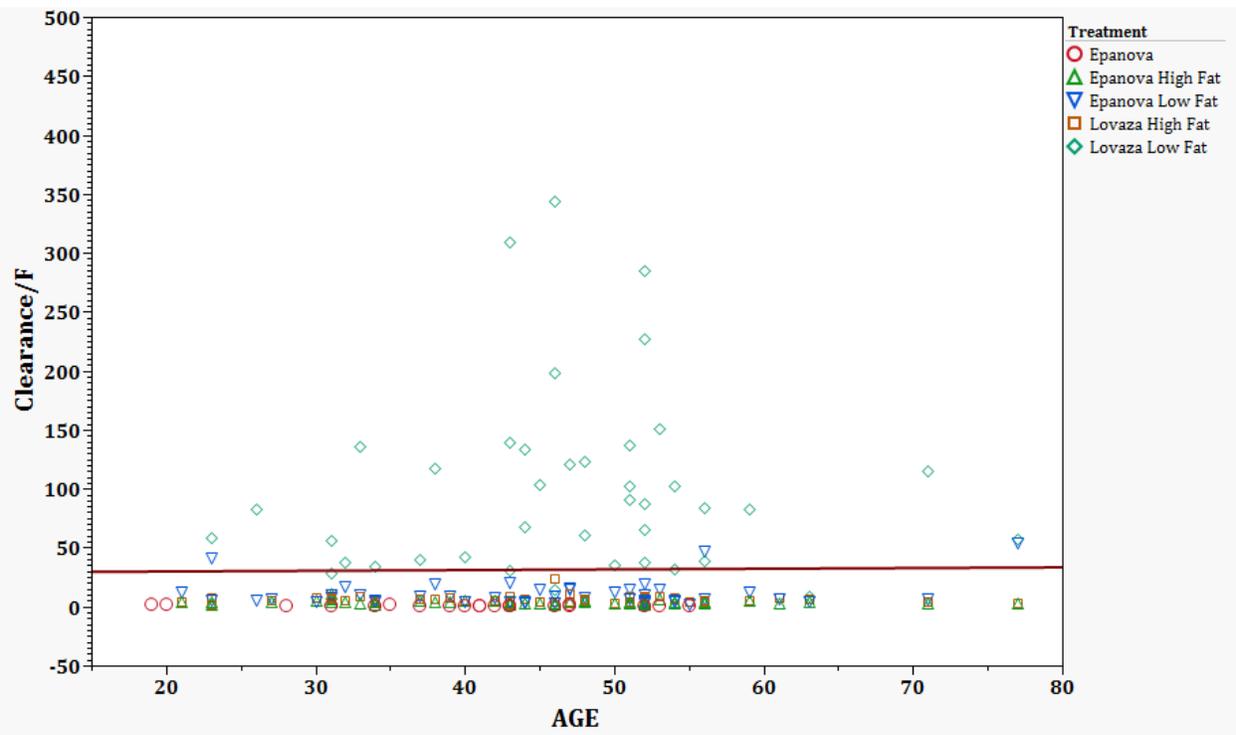


Figure 16 Scatter Plot for Clearance vs. Age for EPA

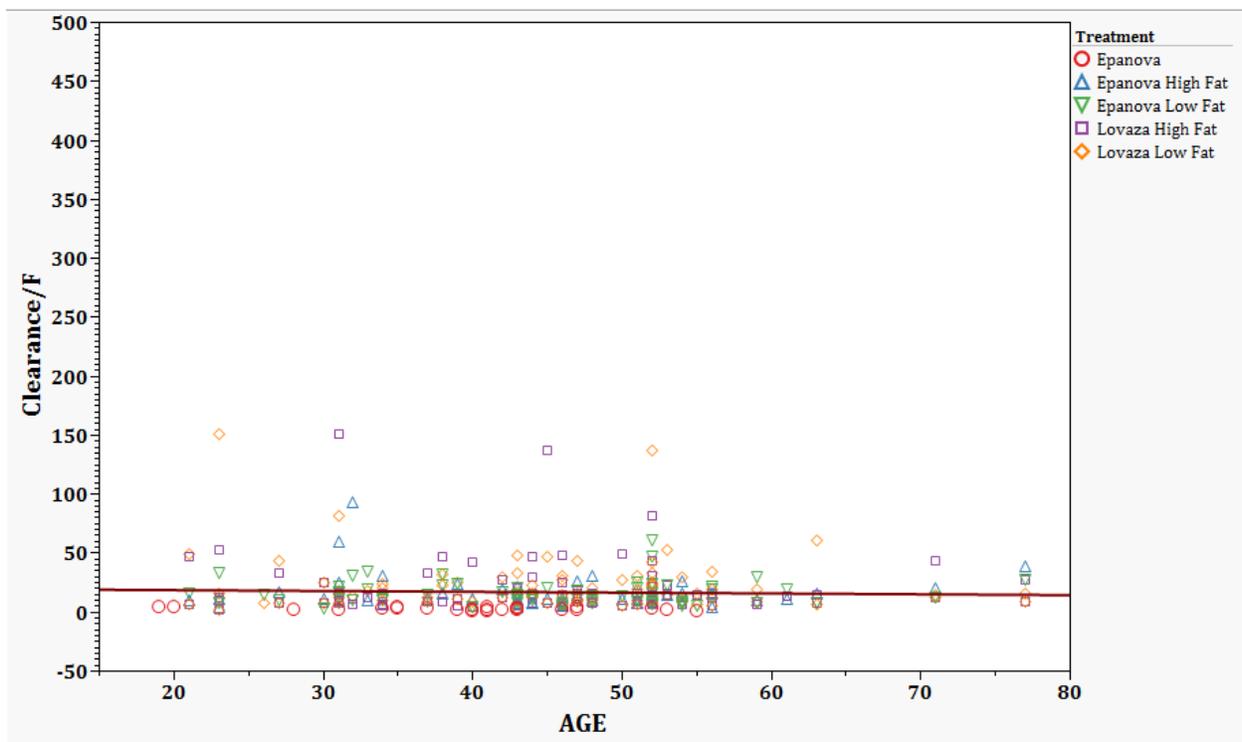


Figure 17 Scatter Plot for Clearance vs. Age for DHA

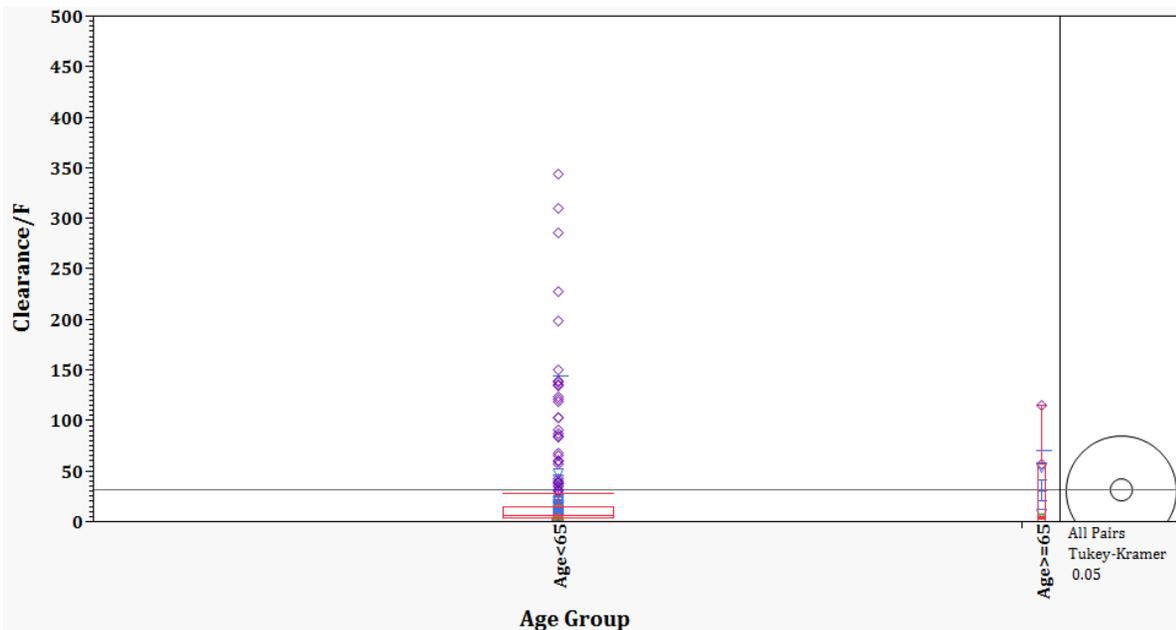


Figure 18 Boxplot of Clearance vs. Age Group for EPA

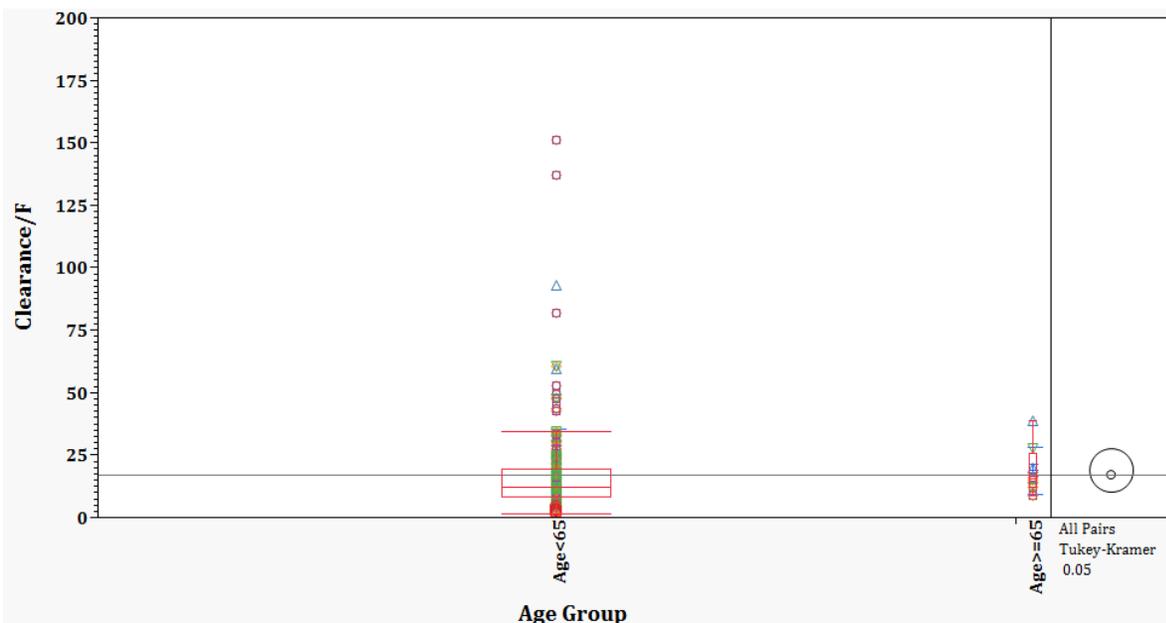


Figure 19 Boxplot of Clearance vs. Age Group for DHA

In addition, based on data from Study OM-EPA-001, there was no effect of age on the half-life of EPA or DHA (Figure 20 and Figure 21, respectively). Classification by age group was not possible since there are only two observations in the group over 65 years of age.

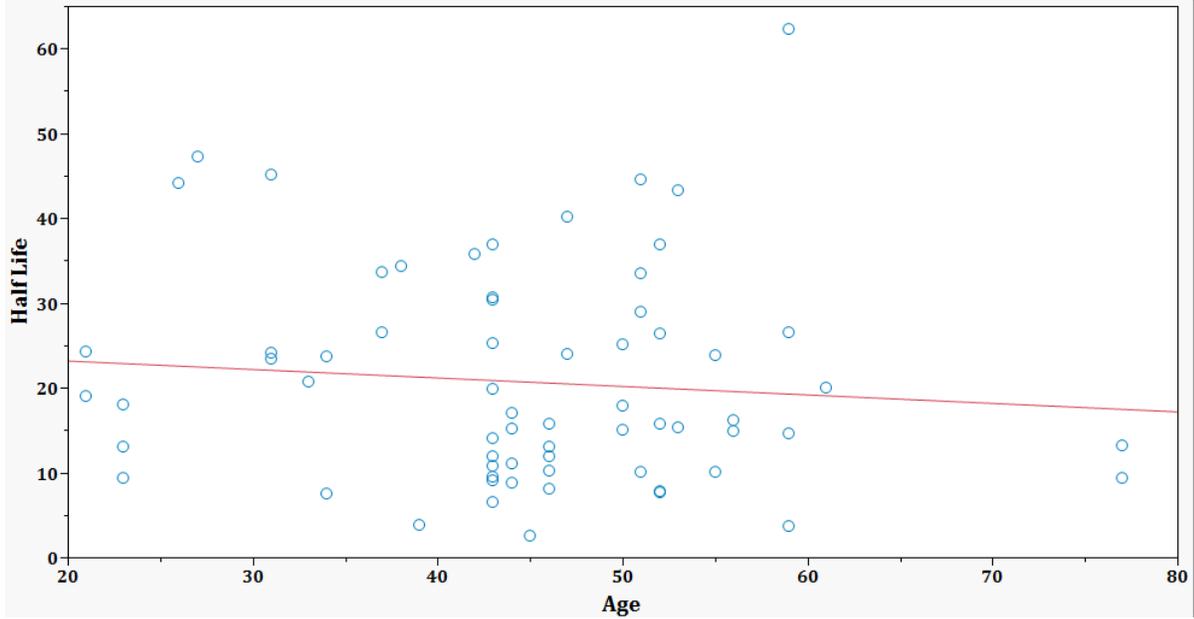


Figure 20 Scatter Plot for $t_{1/2}$ vs. Age for EPA

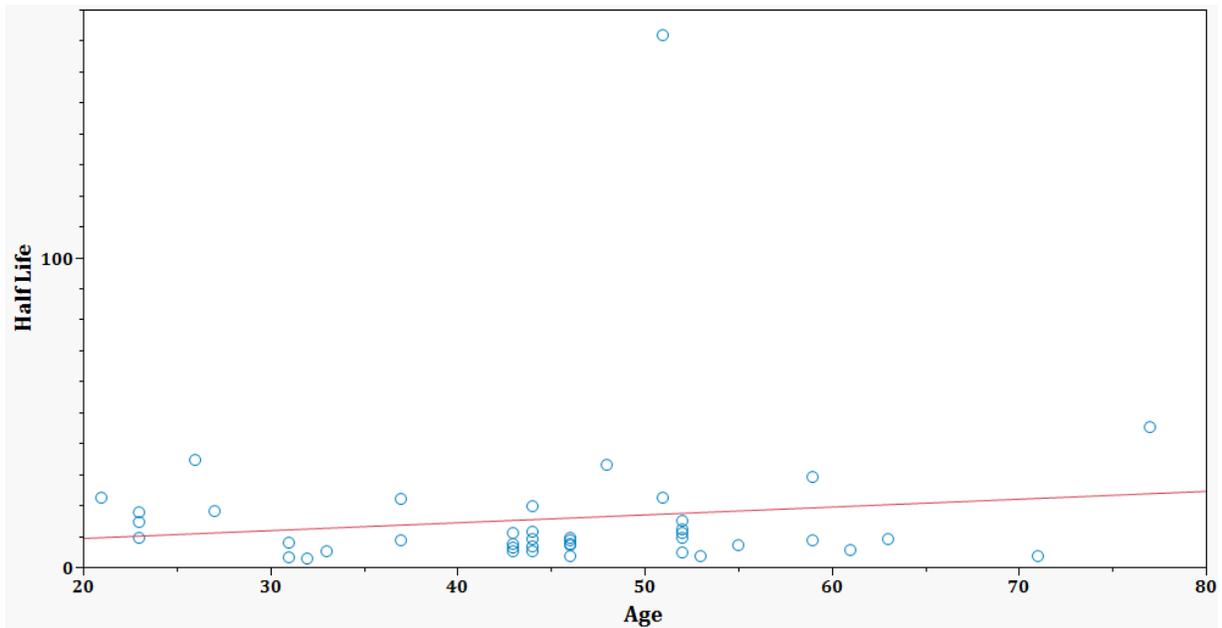


Figure 21 Scatter Plot for $t_{1/2}$ vs. Age for DHA

2.4.1.2 Gender and Race

In the pooled analysis of EPA based upon data from studies OM-EPA-001 and OM-EPA-006, no isolated effects of gender or race were identified. Apparent clearance of EPA ([Figure 22](#)) and DHA ([Figure 23](#)) were similar for male and female subjects.

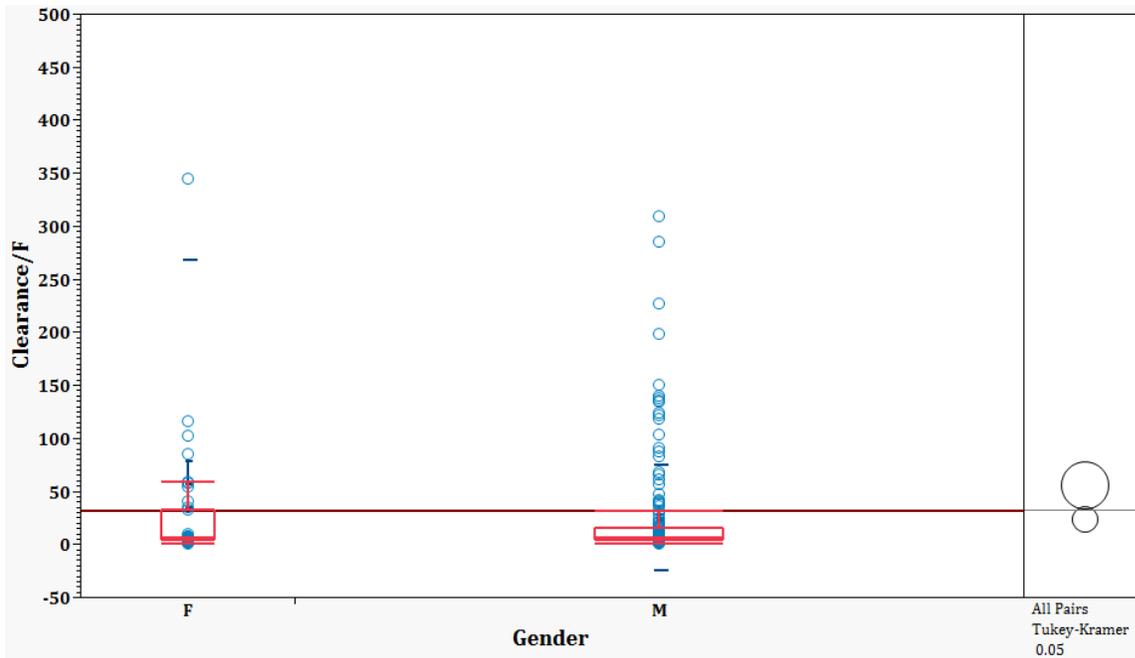


Figure 22 Boxplot of Clearance on Gender for EPA

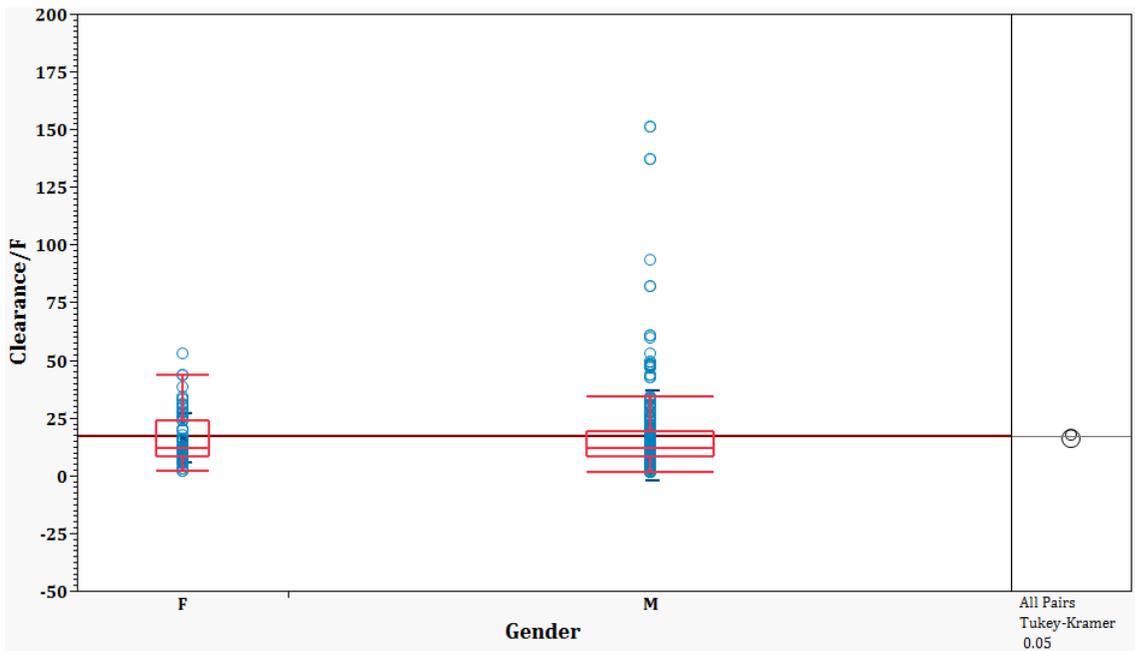


Figure 23 Boxplot of Clearance on Gender for DHA

Similarly apparent clearance of EPA ([Figure 24](#)) and DHA ([Figure 25](#)) were similar across the race groups examined, Caucasian, Black and Asian.

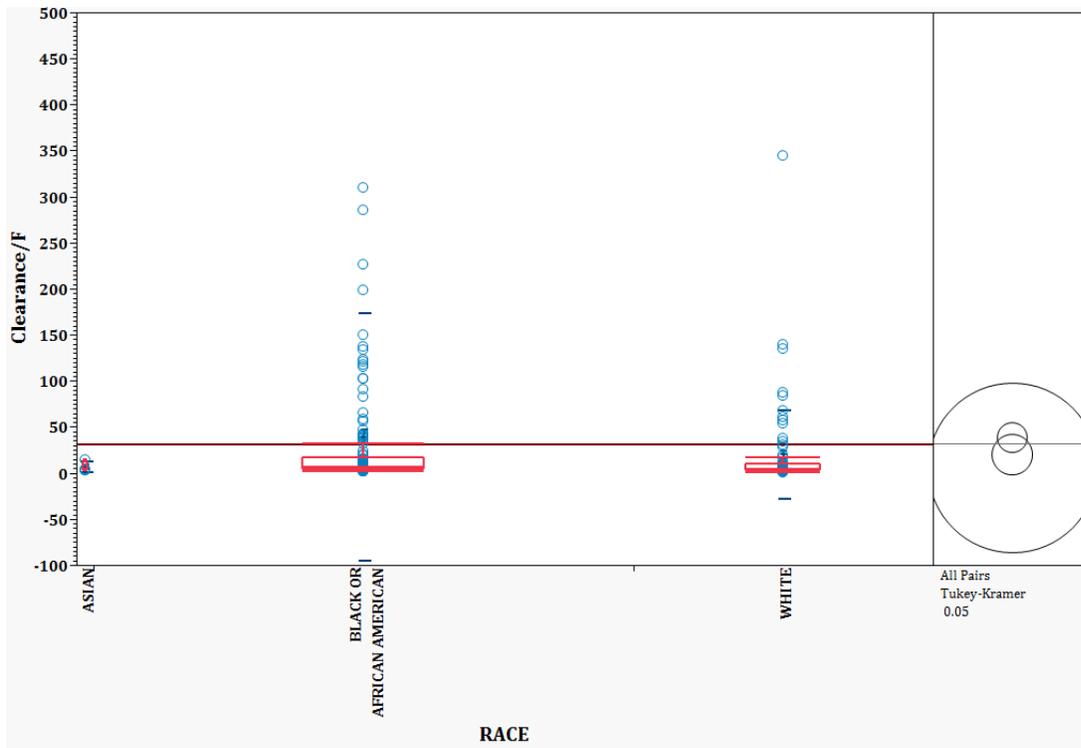


Figure 24 Boxplot of Clearance on Race for EPA

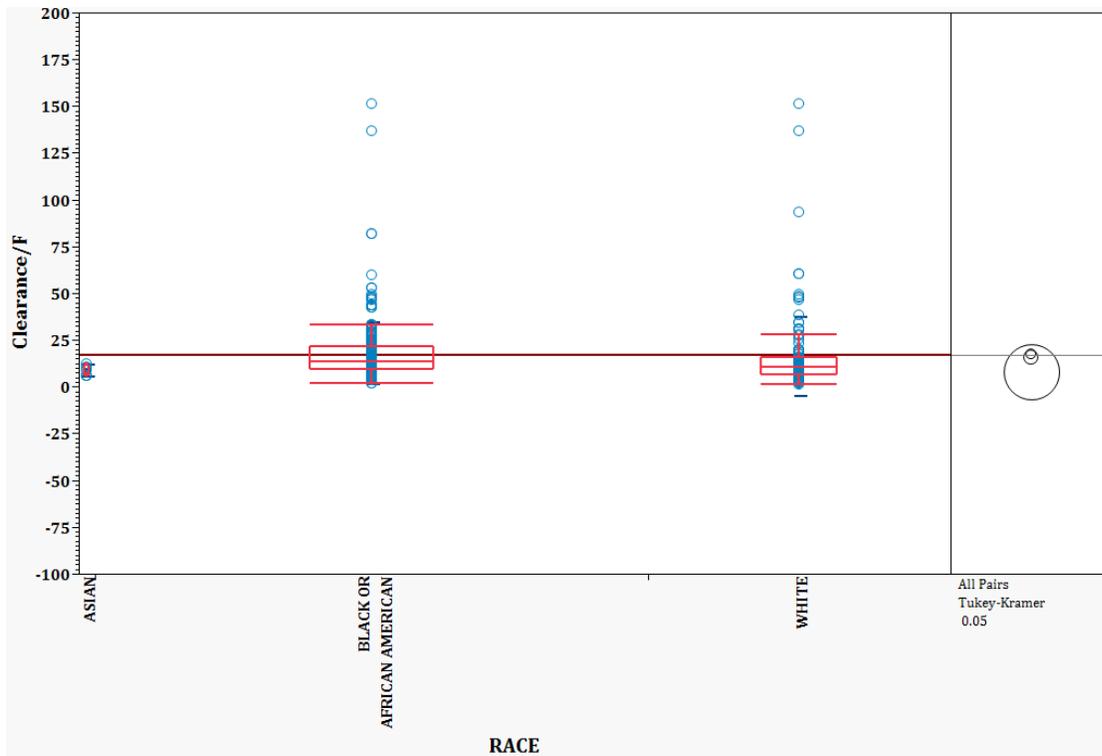


Figure 25 Boxplot of Clearance on Race for DHA

2.4.1.3 Body Weight

In the pooled analysis of EPA based upon data from studies OM-EPA-001 and OM-EPA-006, no isolated effects of body weight were identified for EPA (Figure 26) or DHA (Figure 27).

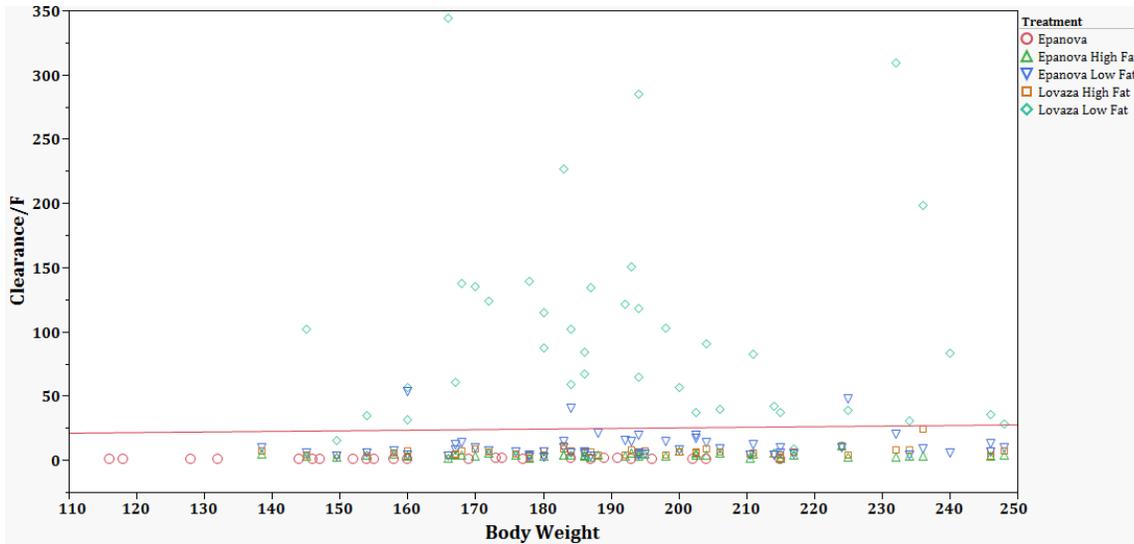


Figure 26 Scatter Plot for Clearance vs. Body Weight for EPA

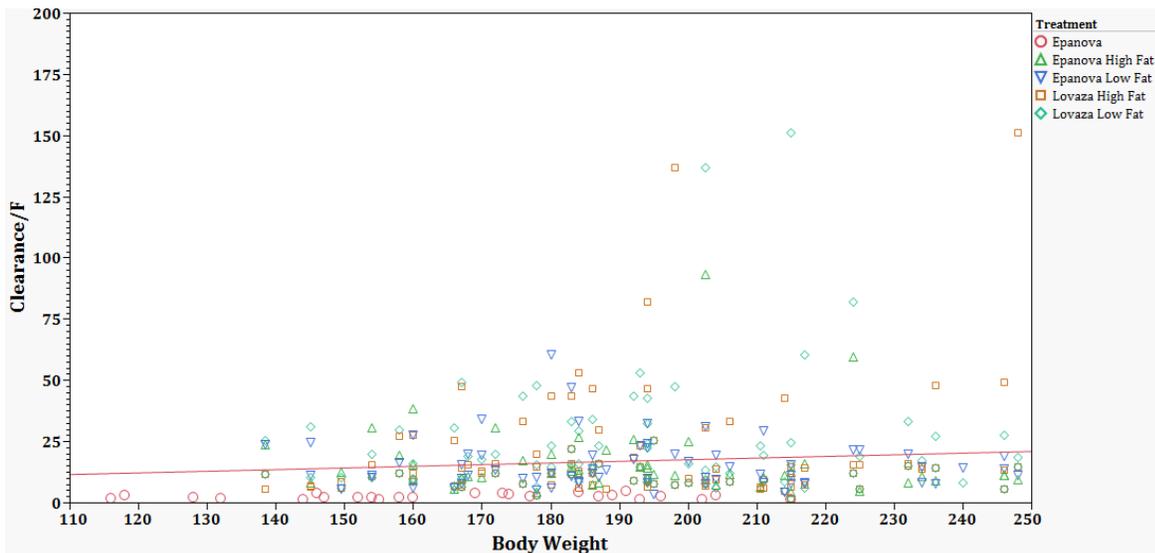


Figure 27 Scatter Plot for Clearance vs. Body Weight for DHA

2.4.2 Does renal function affect Epanova pharmacokinetics?

Epanova has not been studied in patients with renal impairment.

2.4.3 Does hepatic dysfunction affect Epanova pharmacokinetics?

Epanova has not been studied in patients with hepatic impairment.

2.5 Extrinsic Factors

2.5.1 Drug-Drug Interactions

2.5.1.1 What is the CYP inhibition potential of Epanova?

The potential inhibitory effect of Epanova on the important human drug metabolizing cytochrome P450s, CYP 1A2, CYP 2A6, CYP 2B6, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, CYP 3A4/5, and CYP 4A11 were assessed *in vitro* in a pooled microsomal preparation in the presence of 10 and 200 μM of Epanova. The sponsor chose the lower dose level to represent the physiological levels of free fatty acids in the liver of healthy individuals. The higher dose was expected to represent levels 100-fold greater than the expected physiological range. The higher dose was also the apparent maximum solubility of Epanova in the test system matrix. The inhibitory effects of Epanova on the catalytic activity of 10 human hepatic CYP450 enzymes are summarized in [Table 13](#).

Table 13 *In vitro* CYP enzyme inhibition potential of Epanova

CYP	Marker Reaction	% Inhibition at 10 μM Omefas® ¹	% Inhibition at 200 μM Omefas® ¹
1A2	7-ethoxyresorufin O-deethylation	4.9 \pm 1.0	82.0 \pm 0.2
2A6	coumarin 7-hydroxylation	-53.9 \pm 32.9	63.3 \pm 7.3
2B6	S-mephenytoin N-demethylation	15.9 \pm 2.7	75.9 \pm 0.9
2C8	paclitaxel 6 α -hydroxylation	26.7 \pm 4.0	89.9 \pm 0.9
2C9	diclofenac 4'-hydroxylation	17.0 \pm 12.0	35.6 \pm 10.0
2C19	S-mephenytoin 4'-hydroxylation	-14.3 \pm 10.0	79.7 \pm 1.8
2D6	bufuralol -hydroxylation	2.0 \pm 3.0	61.6 \pm 4.9
2E1	chlorzoxazone 6-hydroxylation	0.0 \pm 2.7	79.1 \pm 1.1
3A4	testosterone 6 β -hydroxylation	-4.2 \pm 3.4	95.1 \pm 1.3
4A11	lauric acid 12-hydroxylation	-4.1 \pm 5.3	44.5 \pm 7.6

¹: mean of triplicates \pm standard error
[Source: Sponsor's report 03101701, Table 23, page 38]

With 10 μM Epanova minor or no inhibition (less than 20 %) was observed for 7-ethoxyresorufin O-deethylation (marker reaction for CYP1A1/2), coumarin 7-hydroxylation (marker reaction for CYP2A6), S-mephenytoin N-demethylation (marker reaction for CYP2B6), diclofenac 4'-hydroxylation (marker reaction for CYP2C9), S-mephenytoin 4'-hydroxylation (marker reaction for CYP2C19), bufuralol hydroxylation (marker reaction for CYP2D6), chlorzoxazone 6'-hydroxylation (marker reaction for CYP2E1), testosterone 6 β -hydroxylation (marker reaction for CYP3A4), and lauric acid 12-hydroxylation (marker reaction for CYP4A11).

With 10 μM Epanova intermediate inhibition (26.7 %) was observed with paclitaxel 6 α -hydroxylation (marker reaction for CYP2C8).

With 200 μM Epanova intermediate inhibition (from 20 to 50 %) was observed for diclofenac 4'-hydroxylation (marker reaction for CYP2C9) and lauric acid 12-hydroxylation (marker reaction for CYP4A11).

With 200 μM Epanova major inhibition (higher than 50 %) was observed for 7-ethoxyresorufin O-deethylation (marker reaction for CYP1A1/2), coumarin 7-hydroxylation (marker reaction for CYP2A6), S-mephenytoin N-demethylation (marker reaction for CYP2B6), paclitaxel 6 α -hydroxylation (marker reaction for CYP2C8), S-mephenytoin 4'-hydroxylation (marker reaction for CYP2C19), chlorzoxazone 6'-hydroxylation (marker reaction for CYP2E1), bufuralol hydroxylation (marker reaction for CYP2D6), and testosterone 6 β -hydroxylation (marker reaction for CYP3A4).

Inhibition of CYP marker reactions in human liver microsomes by Epanova is shown in [Figure 28](#).

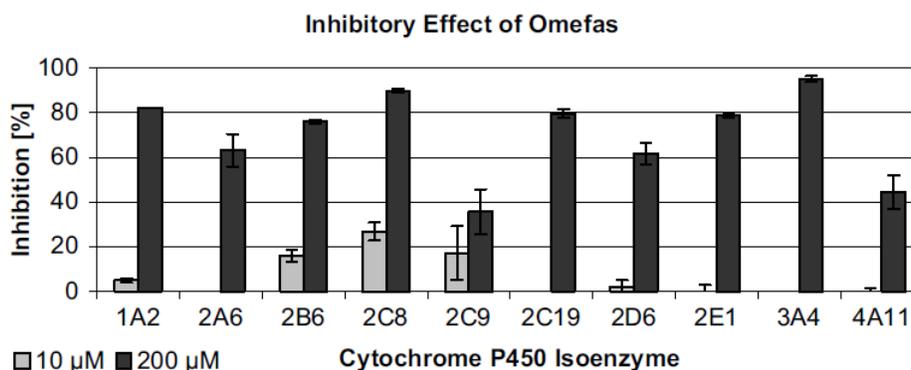


Figure 28 Inhibition of CYP Marker Reactions in Human Liver Microsomes by Epanova

[Source: Sponsor's report 03101701, Figure 1, page 11]

Based on the results of the above study, the sponsor further examined the *in vitro* inhibition potential of Epanova for 2B6, 2C8, and 2C9 using pooled human liver microsomes over the Epanova concentrations of 0.1, 1, or 10 μM . The lowest concentration (0.1 μM) represents already a higher value than the actual value of serum concentration for unbound free fatty acid, whereas the higher concentrations (1 μM , 10 μM) span a safety margin of up to 100-fold of the physiologically relevant concentration. The inhibition rates of the individual enzyme reactions by Epanova are summarized in [Table 14](#), and [Figure 29](#). The results from this study are in line with the results observed with this product class.

Table 14 Inhibition of CYP Marker Reactions by Epanova and Positive Controls

CYP	Marker Reaction	0.1 μM Omefas® ¹	1 μM Omefas® ¹	10 μM Omefas® ¹	Positive control ²
2B6	S-mephenytoin N-demethylation	4.1 ± 14.2	2.5 ± 11.2	2.5 ± 13.9	81.5 ± 2.8
2C8	paclitaxel 6 α -hydroxylation	9.3 ± 11.9	-1.8 ± 10.3	12.7 ± 10.2	87.1 ± 1.3
2C9	diclofenac 4'-hydroxylation	-5.6 ± 16.9	-8.3 ± 14.7	-11.9 ± 17.7	52.5 ± 8.3

¹: mean of triplicates ± standard error

²: positive controls: 50 μM Triethylphenylphosphoramidate (CYP2B6); 10 μM Quercetin (CYP2C8); 1 μM Sulfaphenazole (CYP2C9)

[Source: Sponsor's report 300101, Table 10, page 25]

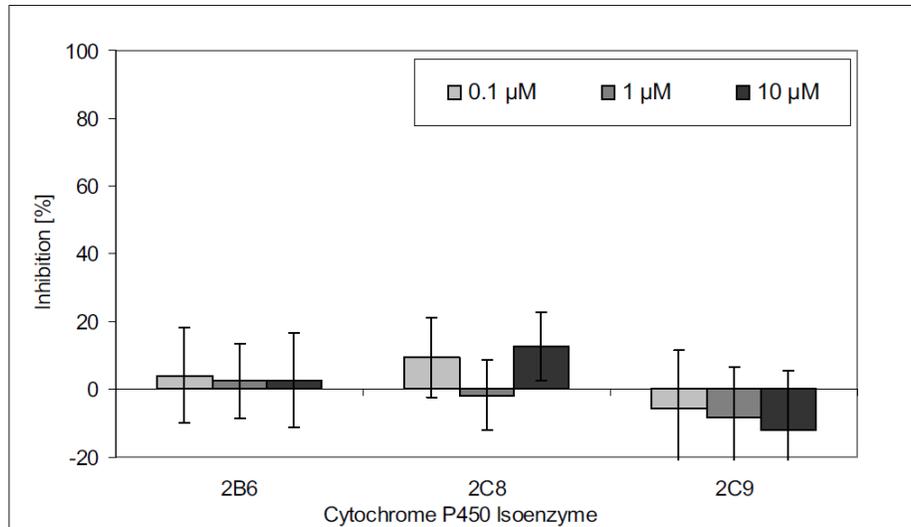


Figure 29 Inhibition of CYP Marker Reactions in Human Liver Microsomes by Epanova at different concentrations

[Source: Sponsor's report 300101, Figure 1, page 10]

The results demonstrate that Epanova exerts no inhibition potential on CYP2B6, CYP2C8 and CYP2C9 in the tested concentration range. This reviewer agrees with the sponsor's conclusion.

2.5.1.2 What is the effect of Epanova co-administration on the pharmacokinetics of other drugs?

Several drug interactions were evaluated by the sponsor with an objective to establish the interaction of those drugs that are likely to be co-administered with Epanova.

2.5.1.2.1 Simvastatin

Study OM-EPA-007 was a drug-drug interaction study that assessed the effect of multiple doses of Epanova on the pharmacokinetics of multiple 40-mg doses of simvastatin. This study employed an open-label, randomized, 2-way crossover design with multiple doses of Epanova and simvastatin in one period, and multiple doses of simvastatin alone in the other period. Low-dose aspirin (81 mg) was also administered daily with simvastatin in both study arms. The study enrolled 52 healthy male (n = 40) and female (n = 12) subjects between 18 and 55 years of age. The body weight ranged between 61.2 and 100.5 kg (males) or 55.3 and 78.0 kg (females) and a body mass index (BMI) between 19.92 and 29.90 kg/m².

On Days 1 through 14, a 40-mg oral dose of simvastatin and an 81-mg dose of aspirin were administered at Hour 0 with (Treatment A) or without (Treatment B) a 4 g (4 x 1 g capsules) oral dose of Epanova with 240 mL of water under fasting conditions.

Mean (SD) simvastatin plasma concentration-time profiles for each treatment are shown in [Figure 30](#).

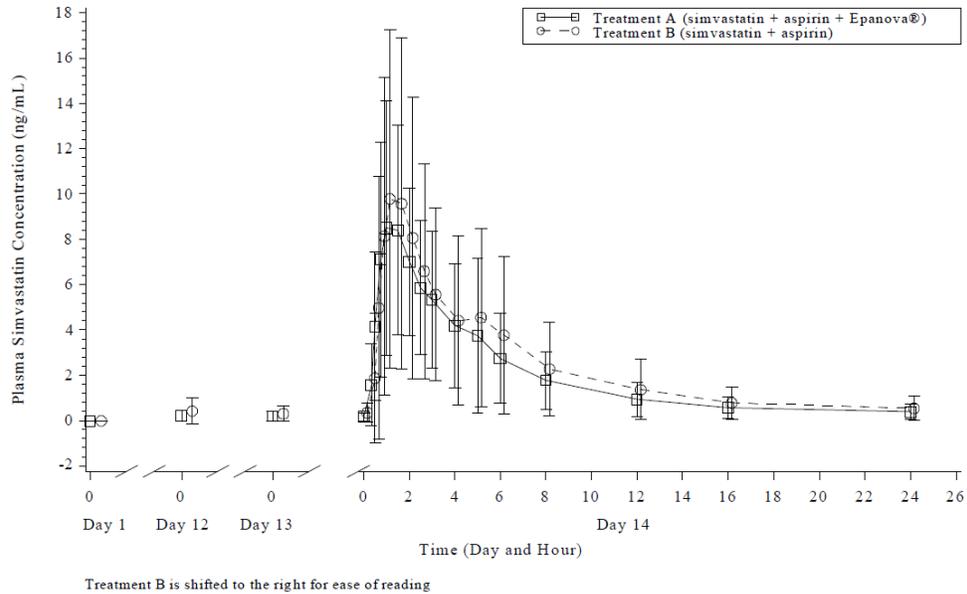


Figure 30 Mean (SD) simvastatin plasma concentrations

[Source: sponsor's study OM-EPA-007, Figure 2, Page 42]

Simvastatin attained steady-state by the 12th day of dosing with both Treatments A and B. On Day 14, peak mean simvastatin concentrations of approximately 8.50 ng/mL and 9.79 ng/mL occurring approximately 1 hour following the administration of Treatments A and B, respectively, were observed. Plasma simvastatin concentrations for both treatments declined in a similar manner, with trough levels being reached on average by 24 hours postdose.

The geometric mean overall ($AUC_{0-\tau}$ and AUC_{0-t}) and peak ($C_{max,ss}$) exposures to plasma simvastatin were comparable following Treatment A (simvastatin + aspirin + Epanova) and Treatment B (simvastatin + aspirin). The mean $C_{min,ss}$ was lower for Treatment A compared to Treatment B, however, the mean average steady-state concentration ($C_{avg,ss}$), percent fluctuation (Fluc) and $T_{max,ss}$ following Treatment A were comparable to that following Treatment B.

The summary of plasma simvastatin PK parameters is presented in [Table 15](#), and the statistical comparisons of plasma simvastatin PK parameters are summarized in [Table 16](#).

Table 15 Summary of Plasma Simvastatin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A	Treatment B
AUC _{0-tau} (ng•hr/mL)	47.9 (45.1) ^a	54.1 (63.9) ^c
AUC _{0-t} (ng•hr/mL)	40.3 (60.7) ^b	45.9 (75.7) ^d
C _{max,ss} (ng/mL)	9.27 (62.1) ^b	9.98 (71.9) ^d
C _{min,ss} (ng/mL)	0.382 (88.0) ^a	0.547 (97.0) ^e
C _{avg,ss} (ng/mL)	2.18 (43.1) ^a	2.66 (65.0) ^c
Fluc (%)	529 (36.5) ^a	516 (45.1) ^c
T _{max,ss} (hr)	1.50 (0.748, 5.00) ^b	1.00 (0.500, 6.00) ^d

AUC_{0-tau}, AUC_{0-t}, and C_{max,ss}, are presented as Geometric Mean (Geometric CV%).
C_{min,ss}, and C_{avg,ss}, and Fluc are presented as Arithmetic Mean (Arithmetic CV%).
T_{max,ss} is presented as Median (Minimum, Maximum).
^a n=41; ^b n=52; ^c n=40; ^d n=51; ^e n=42.

Treatment A: Co-administration of an oral dose of 4 g of Epanova[®] with 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.
Treatment B: An oral dose of 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.

[Source: sponsor's study OM-EPA-007, Table 4, Page 44]

Table 16 Summary of the Statistical Comparisons of Plasma Simvastatin Pharmacokinetic Parameters

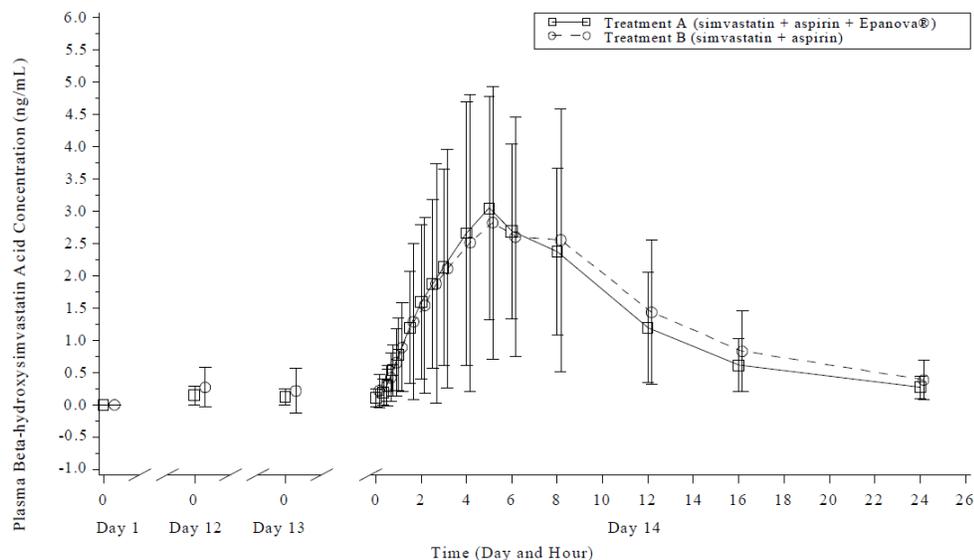
Pharmacokinetic Parameter	Geometric LS Means		% Mean Ratio	90% Confidence Intervals
	Treatment A Test	Treatment B Reference		
AUC _{0-t} (ng•hr/mL)	40.27	46.04	87.47	80.19 - 95.41
AUC _{0-tau} (ng•hr/mL)	45.54	52.00	87.56	78.86 - 97.23
C _{max,ss} (ng/mL)	9.27	10.12	91.61	82.82 - 101.33

AUC_{0-tau}: n = 41 for Treatment A and n = 40 for Treatment B.
AUC_{0-t}: n = 52 for Treatment A and n = 51 for Treatment B.
C_{max,ss}: n = 52 for Treatment A and n = 51 for Treatment B.
Subject 6 was dropped from the study by the Principal Investigator on Day 1 of Period 2 (Treatment B) due to elevated lab values.
Parameters were ln-transformed prior to analysis.
Geometric Mean values for Treatment A and Treatment B are the exponentiated (back-transformed) LSMs from the ANOVA.
Geometric Mean Ratio = 100*(test/reference)

Treatment A: Co-administration of an oral dose of 4 g of Epanova[®] with 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.
Treatment B: An oral dose of 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.

[Source: sponsor's study OM-EPA-007, Table 5, Page 45]

Mean (SD) beta-hydroxysimvastatin plasma concentration-time profiles for each treatment are shown in [Figure 31](#).



Treatment B is shifted to the right for ease of reading

Figure 31 Mean (SD) beta-hydroxysimvastatin plasma concentrations

[Source: sponsor's study OM-EPA-007, Figure 4, Page 46]

Beta-hydroxysimvastatin attained steady-state by the 12th day of dosing with both Treatments A and B. On Day 14, peak mean beta-hydroxysimvastatin concentrations of approximately 3.05 ng/mL and 2.82 ng/mL occurring approximately 5 hours following the administration of Treatments A and B, respectively, were observed. Plasma beta-hydroxysimvastatin concentrations for both treatments declined in a similar manner, with trough levels being reached on average by 24 hours postdose.

The geometric mean overall (AUC_{0-tau} and AUC_{0-t}) and peak ($C_{max,ss}$) exposures to plasma beta-hydroxysimvastatin were comparable following Treatment A (simvastatin + aspirin + Epanova) and Treatment B (simvastatin + aspirin). The mean $C_{min,ss}$ was lower and the percent fluctuation (Fluc) was higher for Treatment A compared to Treatment B, however, the mean average steady-state concentration ($C_{avg,ss}$), and $T_{max,ss}$ following Treatment A were comparable to that following Treatment B.

The summary of plasma β -OH simvastatin PK parameters is presented in [Table 17](#), and the statistical comparisons of plasma β -OH simvastatin PK parameters are summarized in [Table 18](#).

Table 17 Summary of Plasma β -Hydroxy Simvastatin Pharmacokinetic Parameters

Pharmacokinetic Parameters	Treatment A	Treatment B
AUC _{0-tau} (ng•hr/mL)	29.6 (51.1) ^a	30.1 (57.5) ^c
AUC _{0-t} (ng•hr/mL)	26.9 (56.1) ^b	28.1 (61.4) ^d
C _{max,ss} (ng/mL)	2.94 (61.6) ^b	2.63 (63.0) ^e
C _{min,ss} (ng/mL)	0.272 (64.9) ^a	0.388 (78.4) ^f
C _{avg,ss} (ng/mL)	1.38 (48.3) ^a	1.47 (68.8) ^c
Fluc (%)	240 (29.6) ^a	196 (26.8) ^c
T _{max,ss} (hr)	5.00 (2.00, 8.00) ^b	5.00 (3.01, 12.0) ^e

AUC_{0-tau}, AUC_{0-t}, and C_{max,ss}, are presented as Geometric Mean (Geometric CV%).
C_{min,ss}, and C_{avg,ss}, and Fluc are presented as Arithmetic Mean (Arithmetic CV%).
T_{max,ss} is presented as Median (Minimum, Maximum).
^a n=45; ^b n=52; ^c n=46; ^d n=50; ^e n=51; ^f n=47.

Treatment A: Co-administration of an oral dose of 4 g of Epanova[®] with 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.
Treatment B: An oral dose of 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.

[Source: sponsor's study OM-EPA-007, Table 7, Page 48]

Table 18 Summary of the Statistical Comparisons of Plasma β -Hydroxy Simvastatin Pharmacokinetic Parameters

Pharmacokinetic Parameter	Geometric LS Means		% Mean Ratio	90% Confidence Intervals
	Treatment A Test	Treatment B Reference		
AUC _{0-t} (ng•hr/mL)	26.86	28.01	95.90	89.27 - 103.02
AUC _{0-tau} (ng•hr/mL)	28.30	29.73	95.20	87.92 - 103.08
C _{max,ss} (ng/mL)	2.94	2.61	112.56	103.48 - 122.43

AUC_{0-tau}: n = 45 for Treatment A and n = 46 for Treatment B.
AUC_{0-t}: n = 52 for Treatment A and n = 50 for Treatment B.
C_{max,ss}: n = 52 for Treatment A and n = 51 for Treatment B.
Subject 6 was dropped from the study by the PI on Day 1 of Period 2 (Treatment B) due to elevated lab values.
Parameters were ln-transformed prior to analysis.
Geometric Mean values for Treatment A and Treatment B are the exponentiated (back-transformed) LSMs from the ANOVA.
Geometric Mean Ratio = 100*(test/reference)

Treatment A: Co-administration of an oral dose of 4 g of Epanova[®] with 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.
Treatment B: An oral dose of 40 mg of simvastatin and 81 mg of aspirin on Days 1-14.

[Source: sponsor's study OM-EPA-007, Table 8, Page 49]

Reviewer Comments:

Concomitant administration of EPA with Simvastatin and aspirin reduced simvastatin total exposure by approximately 13%. Information from the product label for simvastatin (Zocor) for similar DDI based exposure reduction indicates that fenofibrate and propranol decrease simvastatin exposure by about 10% and 20%, respectively. No dosing adjustment was recommended when coadministering simvastatin with fenofibrate or propranol. Similarly, no dosing adjustment is recommended when administering simvastatin with Epanova.

2.5.1.2.2 Aspirin

Though the main objective of Study OM-EPA-007 was to evaluate the drug-drug interaction between Epanova and simvastatin, the effect of Epanova on aspirin co-administered with simvastatin was also evaluated.

Aspirin was assayed by the VerifyNow aspirin assay. The VerifyNow-Aspirin assay is a qualitative assay to aid in the detection of platelet dysfunction due to aspirin ingestion in citrated whole blood for the point of care or laboratory setting. This assay is not for use in patients with underlying congenital platelet abnormalities, patients with non-aspirin induced acquired platelet abnormalities or in patients receiving non-aspirin anti-platelet agents.

The VerifyNow System is a turbidimetric based optical detection system which measures platelet induced aggregation as an increase in light transmittance. The system consists of a stand-alone instrument and disposable assay device with reagents based on microbead agglutination technology. The quality control system includes an electronic quality control, an assay device internal control, and two levels of external, wet quality control controls. The instrument controls assay sequencing, establishes the assay temperature, controls the reagent-sample mixing for the required duration, determines the degree of platelet function, displays the results and status information to the user, and performs self-diagnostics.

The assay device contains a lyophilized preparation of human fibrinogen coated beads, platelet agonist, a peptide, bovine serum albumin, buffer, and stabilizer. The patient sample is citrated whole blood, which is automatically dispensed from the blood collection tube into the assay device by the instrument, with no blood handling required by the user.

Fibrinogen-coated microparticles are used in the VerifyNow-Aspirin assay device to bind activated platelet GP IIb/IIIa receptors. When the activated platelets are exposed to the fibrinogen-coated microparticles, aggregation occurs in proportion to the number of activated platelet receptors. To ensure consistent and uniform activation of the platelets, the agonist arachidonic acid is incorporated into the assay device. The VerifyNow-Aspirin Assay reports results in Aspirin Reaction Units (ARU).

The reference range for pre-aspirin samples is 620-672 ARU (2.5 to 97.5 percentile)

Mean (SD) VerifyNow aspirin assay results at check-in (baseline) prior to treatment, check-out (Day 15) post-treatment, and change from baseline following Treatment A (simvastatin + aspirin + Epanova) and Treatment B (simvastatin + aspirin), are presented in [Figure 32](#).

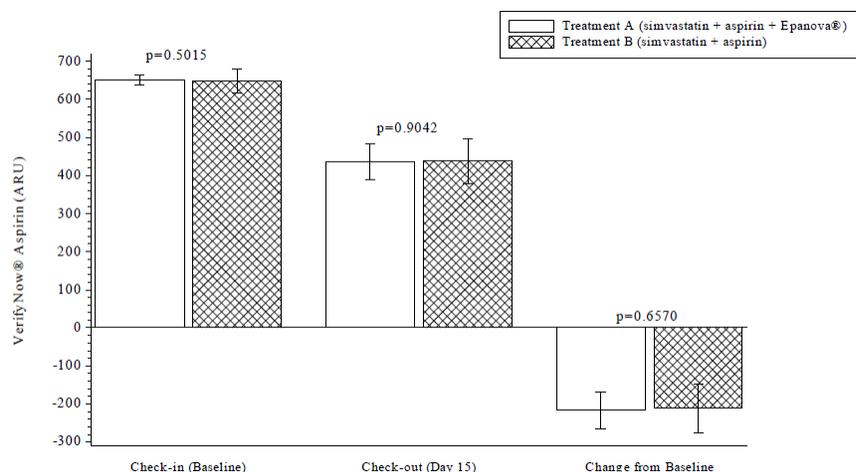


Figure 32 Mean (SD) VerifyNow Aspirin Assay Results

[Source: sponsor's study OM-EPA-007, Figure 13, Page 59]

The mean VerifyNow Aspirin result at check-in (baseline) of 651 ARU prior to Treatment A (simvastatin + aspirin + Epanova), was comparable ($p > 0.05$) to the 649 ARU observed at check-in (baseline) prior to Treatment B (simvastatin + aspirin). Similarly, the mean of 435 ARU observed at check-out (Day 15) post-Treatment A, was comparable to the mean of 437 ARU observed at check-out (Day 15) post-Treatment B. The post-treatment decreases, with respect to baseline, of 216 ARU and 211 ARU following Treatments A and B, were comparable ($p > 0.05$).

Reviewer Comments on results of the study:

This study demonstrated that the daily coadministration of Epanova 4 grams with simvastatin 40 mg with did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or its major active metabolite, β -hydroxy simvastatin at steady state. In addition, this study concluded that concomitant administration of Epanova does not alter the anti-platelet effect of low-dose aspirin. However, the concomitant administration of simvastatin and aspirin along with Epanova does not offer the opportunity for a clean evaluation of the drug-drug interaction potential of Epanova on either simvastatin or aspirin. Any confounding effects of simvastatin and aspirin on each other in presence of Epanova is unknown.

2.5.1.2.3 Warfarin

Study OM-EPA-006 was a drug-drug interaction study that assessed the effect of multiple doses of Epanova on the PK and PD of a single 25 mg dose of warfarin. This study employed an open-label, 2-cohort parallel design. Results from cohort 1 was used to assess the drug-drug interaction potential of Epanova on warfarin. Subjects in cohort 2 were administered multiple doses of 4g Lovaza (EPA+DHA).

Warfarin, 25 mg was administered as a single-dose following an overnight fast in Treatment A. In Treatment B, a 4 g dose of Epanova was administered on Days 8 – 28, co-administered with a single 25 mg dose of warfarin on Day 22. All doses were administered approximately 30 minutes following the start of a low-fat breakfast, with the exception of the Day 22 dose which was co-administered with warfarin following an overnight fast. The study enrolled 52 healthy male ($n = 37$) and female ($n = 15$) subjects between 18 and 55 years of age. The body weight ranged between

52.4 and 97.5 kg (males) or 57.9 and 85.6 kg (females) and a body mass index (BMI) between 21.21 and 29.84 kg/m².

The mean (SD) concentration profiles for (S)-warfarin, (R)-warfarin and Epanova are shown in [Figure 33](#) below.

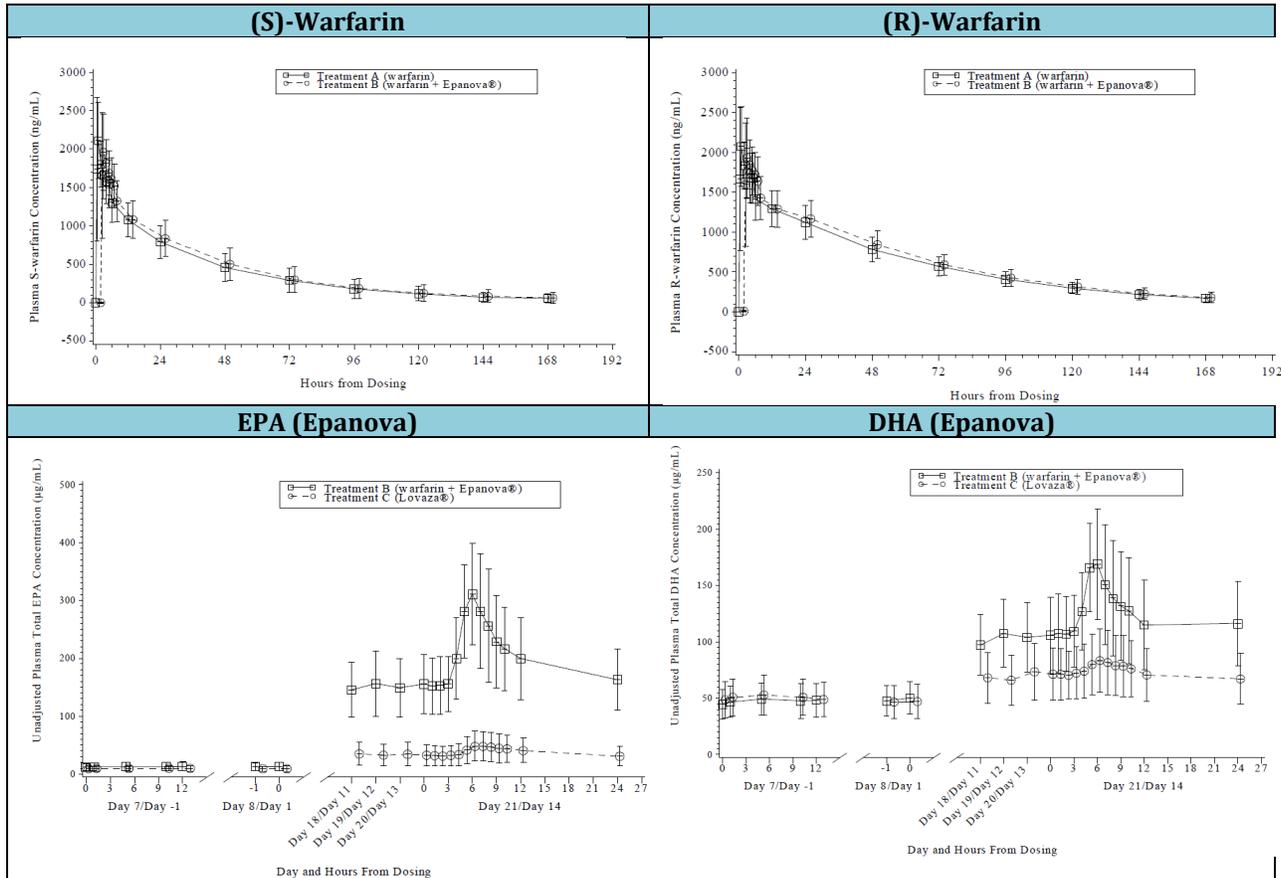


Figure 33 Pharmacokinetic profiles of (S)-warfarin, (R)-warfarin and Epanova

[Source: Sponsor's report OM-EPA-006, Figures 4, 2, 7, pages 49, 50, 52]

Statistical analysis of pharmacokinetic parameters summarized in [Table 19](#) below for S-warfarin and [Table 20](#) for R-warfarin showed that the 90% CIs for C_{max} and AUC of S-warfarin and R-warfarin were within the protocol-specified range of 80- 125%, demonstrating the lack of pharmacokinetic interaction on peak and systemic exposure.

Table 19 Treatment ratio estimates of warfarin plus Epanova versus warfarin alone with 90% confidence interval (analysis for pharmacokinetic population) – S-warfarin

Parameter	Geometric LS Means		% Mean Ratio	Confidence Intervals
	Treatment B Test	Treatment A Reference		90% Confidence
AUC _(0-t) (ng*hr/mL)	64810.54	62845.55	103.13	100.32 - 106.01
AUC _(0-inf) (ng*hr/mL)	68346.95	66141.98	103.33	100.27 - 106.49
C _{max} (ng/mL)	2081.49	2302.04	90.42	85.28 - 95.86

Parameters were ln-transformed prior to analysis.
 Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
 % Mean Ratio = 100*(test/reference)

Treatment A: A single 25 mg dose of warfarin on Day 1 (fasted).
 Treatment B: A 4 g dose of Epanova® on Days 8 - 28 (fed), co-administered with a single 25 mg dose of warfarin on Day 22 (fasted).

[Source: Sponsor's report OM-EPA-006, Table 9, page 68]

Table 20 Treatment ratio estimates of warfarin plus Epanova versus warfarin alone with 90% confidence interval (analysis for pharmacokinetic population) – R-warfarin

Parameter	Geometric LS Means		% Mean Ratio	Confidence Intervals
	Treatment B Test	Treatment A Reference		90% Confidence
AUC _(0-t) (ng*hr/mL)	104659.28	101257.14	103.36	100.81 - 105.97
AUC _(0-inf) (ng*hr/mL)	119006.62	114785.21	103.68	100.61 - 106.84
C _{max} (ng/mL)	2052.48	2240.29	91.62	87.44 - 96.00

Parameters were ln-transformed prior to analysis.
 Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
 % Mean Ratio = 100*(test/reference)

Treatment A: A single 25 mg dose of warfarin on Day 1 (fasted).
 Treatment B: A 4 g dose of Epanova® on Days 8 - 28 (fed), co-administered with a single 25 mg dose of warfarin on Day 22 (fasted).

[Source: Sponsor's report OM-EPA-006, Table 7, page 67]

The pharmacodynamic endpoints measured in this study were the maximum international normalized ratio (INR_{max}) over 168 hours postdose and INR AUC₍₀₋₁₆₈₎ when warfarin was administered with and without Epanova. Plots of mean (SD) warfarin PT INR are presented in linear scale in [Figure 34](#).

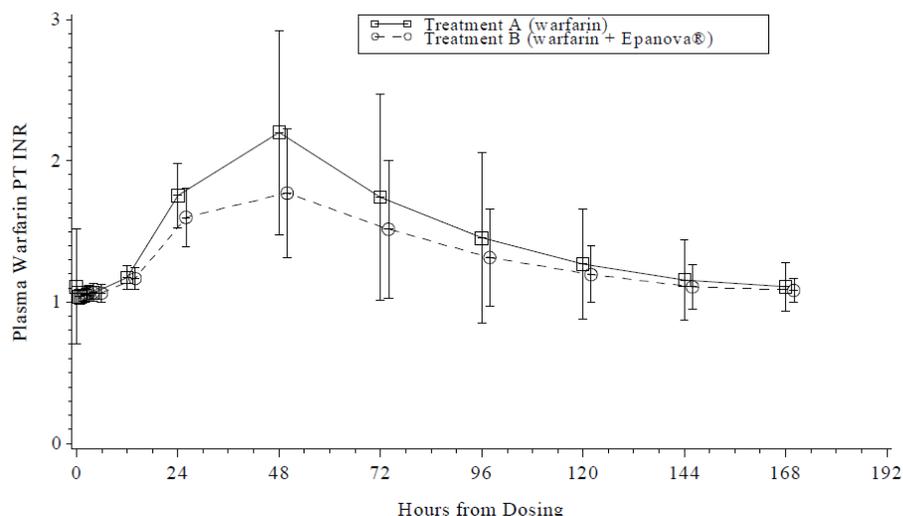


Figure 34 Average international normalized ratio over C_{max} and $AUC_{(0-\tau)}$ for Following Warfarin alone or Warfarin co-administered with Epanova

[Source: Sponsor's report OM-EPA-006, Figure 5, page 51]

The statistical comparisons of plasma warfarin PD parameters are summarized in [Table 21](#).

Table 21 Summary of the Statistical Comparisons of Plasma Warfarin Pharmacodynamic Parameters

Parameter	Geometric LS Means		% Mean Ratio	Confidence Intervals
	Treatment B Test	Treatment A Reference		90% Confidence
INR $AUC_{(0-168)}$	224.91	244.87	91.85	89.85 - 93.90
INR _{max}	1.77	2.11	84.02	80.96 - 87.19

Parameters were ln-transformed prior to analysis.
 Geometric least-squares means (LSMEANS) are calculated by exponentiating the LSMEANS from the ANOVA.
 % Mean Ratio = 100*(test/reference)
 Subject 23 was excluded from statistical analysis for not completing the study.

Treatment A: A single 25 mg dose of warfarin on Day 1 (fasted).
 Treatment B: A 4 g dose of Epanova® on Days 8 - 28 (fed), co-administered with a single 25 mg dose of warfarin on Day 22 (fasted).

[Source: Sponsor's report OM-EPA-006, Table 11, page 69]

The 90% CIs of the ln-transformed INR_{max} and INR $AUC_{(0-168)}$ for warfarin PT INR for Treatment B (warfarin + Epanova) versus Treatment A (warfarin) were within 80% - 125%. The pharmacodynamic effect of warfarin as determined by INR profiling did not suggest an impact of concomitant Epanova treatment. The maximum observed change in INR was change from 2.11 to 1.77.

Reviewer Comments:

Epanova administered at a dose of 4 grams/day at steady-state did not significantly affect the single dose AUC or C_{max} of R- and S- warfarin or the anti-coagulation pharmacodynamics (PT INR) of 25 mg warfarin. This study evaluated the drug-drug interaction potential of a steady-state administration of Epanova on a single-dose administration of warfarin. The interaction potential of steady-state

administration of Epanova on a steady-state administration of warfarin is unknown. While no dose adjustment for warfarin is required when co-administered with Epanova based on lack of single-dose pharmacokinetic or pharmacodynamic interaction, frequent monitoring of INR in patients on warfarin and/or coumarin derivatives, as well as following of instructions in the warfarin product monograph for appropriate monitoring and dose adjustment is recommended at the time of initiation or ending of Epanova treatment.

2.6 General Biopharmaceutics

2.6.1 What is absolute bioavailability and disposition of Epanova?

Not applicable.

2.6.2 Is bioequivalence established between the to-be-marketed formulation and the Phase 3 trial formulation and how does it relate to the overall product development?

Proposed commercial formulation is the same as the one used in Phase I, II and III studies. The drug product composition is described in [Table 22](#). An overview on the formulation history is shown in [Table 23](#).

Table 22 Drug Product Composition of Epanova

Table 3.2.P.1-1. Drug Product Composition			
Ingredient	Function	Specification	Weight Per Capsule (mg)
Omefas ^a	Active ingredient	3.2.S.4.1	1,000
Capsule Shell	Capsule shell	USP/NF, Ph. Eur.	(b) (4)
Gelatin (porcine type A, (b) (4))			
Sorbitol (b) (4)			
Glycerol (b) (4)			
Purified Water			
Total shell weight			
Capsule Coating	(b) (4)	NF, Ph. Eur., JP	(b) (4)
Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4)			
Talc			
Titanium dioxide			
Iron oxide red			
Polysorbate 80			
Carboxymethylcellulose sodium			
Purified water			
Total coating weight			
Printing Ink ^d	Identification	USP/NF	-
Total capsule weight			1,470.0
^a = (b) (4)			
^b = (b) (4)			
^c = (b) (4)			
^d = The qualitative composition of the ink is provided in Table 3.2.P.1-2			
^e = (b) (4)			

Table 3.2.P.1-2. Qualitative Composition of (b) (4) White Monogramming Ink	
Ingredient	Reference to Standard
Pharmaceutical (b) (4) Glaze - (b) (4)	USP/NF
Titanium Dioxide	USP/NF
N-Butyl Alcohol	USP/NF
Propylene Glycol	USP/NF
Isopropyl Alcohol	USP/NF

The following processing aids are used during manufacturing but do not remain in the drug product.

Table 3.2.P.1-3. Processing Aids		
Processing Aid	Function	Specification
(b) (4)		

[Source: sponsor's Description and Composition of the Drug product, module 3.2.P.1, Tables 3.2.P.1-1 - 3.2.P.1-3, Pages 3-4]

Table 23 Formulation history of Epanova

Table 3.2.P.2.2-5. Clinical Trial Formulations		
Formulation	Manufacturing History	Clinical Use
(b) (4)	(b) (4)	Phase 1 (SPC-275-4)
		Phase 1 (SPC-275-4) Phase 2 (EPIC-3) Phase 3 (EPIC-1, EPIC-2, EPIC-1E)
		Phase 1 (OM-EPA-006, OM-EPA-007) Phase 2 (ECLIPSE Trial OM-EPA-001) Phase 3 (EVOLVE Trial OM-EPA-003, ESPRIT Trial OM-EPA-004)
^a =	(b) (4) capsule	
^b =	SGC soft gelatin capsule	

Formulation ^a	Batch Number ^b	Batch Size ^c (capsules)	Date of Mfg.	Site of Mfg.	DS Lot #	Type of Study/ Study Number
B	99X003A	(b) (4)			PP5/723	SPC-275-4 Study
A	00B20X				PP4/1063	
A	00D13X					
B	02X002A				14963	EPIC 1, EPIC 2, and EPIC 3
B	02X002B					
B	02X002C					
B	02X002D					
B	02X002E					
B	04X004A				102631	EPIC 1 and EPIC 2
B	04X005A					EPIC 2
B	04X006A					EPIC 1E, EPIC 2
B	04X007A				102632	EPIC 1E, EPIC 3
C	1433670001-01				36355	ECLIPSE Trial (OM-EPA-001)
C	1442210001-09				36395	Epanova stability (OSP 02 and OSP 03), EVOLVE Trial (OM-EPA-003), Two drug interaction studies (OM-EPA-006 and OM-EPA-007)
C	1455620001-04				37225	Epanova stability (OSP 09 and OSP 12) ESPRIT Trial (OM-EPA-004)

^a = Refer to [Table 3.2.P.2.2-5](#) for designations for Formulations A, B and C. (b) (4)

[Source: sponsor's Pharmaceutical Development, Drug Product, module 3.2.P.2, Tables 3.2.P.2.2-5 - 3.2.P.2.2-6, Pages 13-14]

2.6.3 What is the effect of food on the bioavailability of the drug

The effect of fasting/low-fat and high-fat meal on the bioavailability of EPA and DHA from a single dose of Epanova was evaluated in Study OM-EPA-001.

The study was a randomized, open-label, 4-way crossover study, with 4 single-dose treatment periods and a minimum 7-day washout in between each treatment. For the washout periods, including the screening period, subjects were instructed to follow the Therapeutic Lifestyle Changes (TLC) diet. Each treatment period consisted of an in-clinic stay for 12 hours, and a 24-hour followup visit. Subjects were given a frozen low-fat dinner (10% of total meal kilocalories) at

Visits 1, 3, 5 and 7 with instructions to consume the meal 12 hours before returning for their next clinic visit. Subjects were instructed to consume only noncaloric beverages during the 12 hr fast before coming to each clinic visit in the morning. Subjects were randomized 1:1 to one of the following treatment period sequences: ELEL or LELE where E=Epanova and L=Lovaza. The meals assigned to each period were fixed: Period 1 was low-fat (~5% of total meal kcal), Period 2 was low-fat, Period 3 was high-fat (30% of total meal kcal) and Period 4 was high-fat. After collection of fasting blood samples (-1.0, -0.5 and 0 hours pre-dose), all subjects were to consume 4 g of either Epanova or Lovaza followed by blood draws at 1, 2, 3, 4, 5, 6, 7, 8, 10 and 12 hours, and the next day at 24 hours. For low-fat Periods 1 and 2, subjects were to skip breakfast, and have a no-fat lunch after the 4 hr blood draw and a low-fat dinner after the last blood draw (12 hr) before leaving the clinic. Subjects were to fast at least 12 hours and return the next day for a 24 hr fasting blood draw. For high-fat Periods 3 and 4, subjects were to eat a high-fat breakfast immediately after the -0.5 hr blood draw, a high-fat lunch after the 4 hr blood draw and a high-fat dinner after the last blood draw (12 hr) before leaving the clinic. Subjects were to fast at least 12 hours and return the next day for a 24 hr fasting blood draw.

EPA: The relative bioavailability of total EPA from Epanova with a fasting/no-fat/low-fat diet was lower than that with a high-fat diet (AUC_{0-t} ratio 41.9% and 55.6%, respectively for adjusted and unadjusted baselines).

Similarly, the relative bioavailability of free EPA was lower when Epanova was administered with fasting/no-fat/low-fat diets in comparison to high-fat diets (ratio 56.6% and 68.7% for adjusted and unadjusted baseline, respectively).

Results of the statistical analysis are shown in [Table 24](#). Plots of free and total EPA by treatment are shown in [Figure 35](#).

Table 24 Summary of ANOVA Results for Total and Free EPA

Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)											
Ln-Transformed data											
Total EPA (µg/mL)											
A vs. B Analysis		Baseline Adjusted					Unadjusted				
		LSM A	LSM B	A/B	90% CI		LSM A	LSM B	A/B	90% CI	
					Lower	Upper				Lower	Upper
Epanova Fasting/No-fat/Low-fat vs. High-fat	Total EPA										
	AUC _{0-t}	456.08	1087.88	41.90 p<0.0001	35.60	49.37	819.98	1474.82	55.60 p<0.0001	50.62	61.07
	AUC _{0-inf}	886.01	2171.43	40.80	31.99	52.04	-	-	-	-	-
	C _{max}	37.50	118.22	31.70	25.53	39.41	54.29	135.36	40.10	34.27	46.94
	Free EPA										
	AUC _{0-t}	4671.67	8250.11	56.60 p<0.0001	47.03	68.18	6972.95	10153.46	68.68 p<0.0001	60.02	78.58
AUC _{0-inf}	5669.14	9072.85	62.50	48.81	79.99						
C _{max}	572.59	1225.63	46.70	36.99	59.00	680.68	1310.69	51.93	42.17	63.95	

Treatment ANOVA p-value presented for AUC_{0-t}.

(Source: Study OM-EPA-001, Table 11.4-2, Page 53 and Table 11.4-5, Page 56)

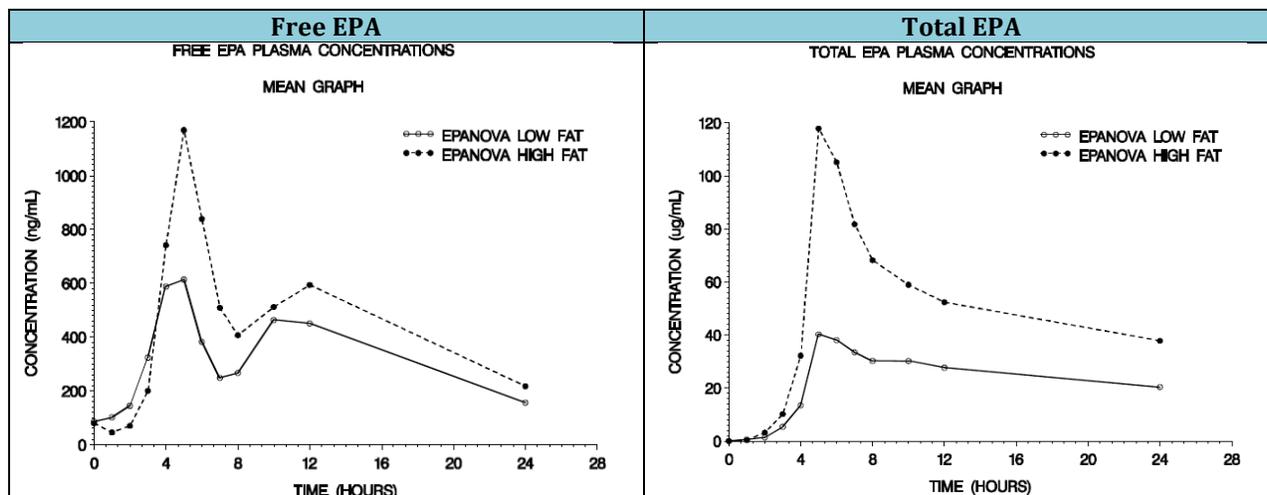


Figure 35 Mean Free and Total EPA Concentrations Following Low-Fat and High-Fat Meals

(Source: Study OM-EPA-001, Figure 14.2.2.3.3, Page 127, and Figure 14.2.5.3.3, Page 214)

DHA: The relative bioavailability of total DHA was comparable when Epanova was administered under low-fat was compared to high-fat conditions (adjusted and unadjusted ratios about 106%, 94% for total DHA and 70%, 101% for free DHA).

Results of the statistical analysis are shown in [Table 25](#). Plots of free and total DHA by treatment are shown in [Figure 36](#).

Table 25 Summary of ANOVA Results for Total and Free DHA

Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)											
Ln-Transformed data											
Total EPA (µg/mL)											
A vs. B Analysis		Baseline Adjusted				Unadjusted					
		LSM A	LSM B	A/B	90% CI		LSM A	LSM B	A/B	90% CI	
Total DHA											
Epanova Fasting/No-fat/Low-fat vs. High-fat	AUC _{0-t}	323.27	303.93	106.40 p=0.5041	91.22	124.02	1689.03	1790.19	94.30 p=0.0098	90.99	97.84
	AUC _{0-inf}	532.23	870.26	61.20	43.21	86.56	-	-	-	-	-
	C _{max}	28.91	52.10	55.50	46.34	66.45	87.53	116.54	75.10	69.53	81.13
	Free DHA										
	AUC _{0-t}	4769.41	6794.48	70.20 p=0.0385	53.12	92.76	18992.78	18822.87	100.90 p=0.8392	93.72	108.64
	AUC _{0-inf}	-	-	-	-	-	-	-	-	-	-
C _{max}	778.65	1286.85	60.50	49.741	73.61	1387.17	1793.19	77.36	67.56	88.58	

Treatment ANOVA p-value presented for AUC_{0-t}.

(Source: Study OM-EPA-001, Table 11.4-3, Page 54 and Table 11.4-6, Page 57)

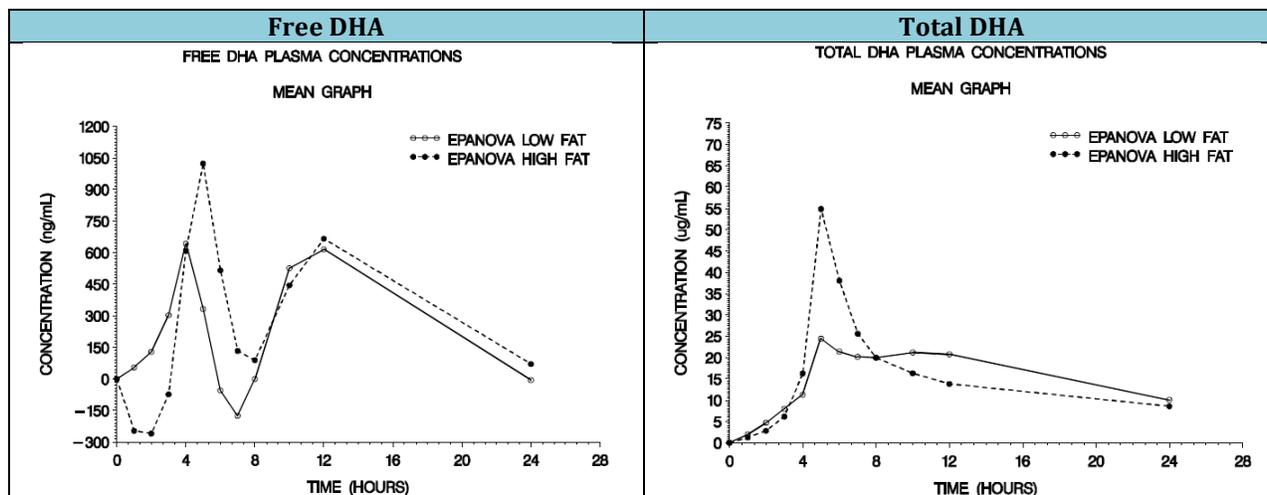


Figure 36 Mean Free and Total DHA Concentrations Following Low-Fat and High-Fat Meals

(Source: Study OM-EPA-001, Figure 14.2.3.3.3, Page 156, and Figure 14.2.6.3.3, Page 243)

Reviewer Comments:

There appears to be food-effect with Epanova. Compared to fasting administration, following administration of Epanova with a high-fat meal, there is an increase in relative bioavailability of total and free baseline adjusted EPA by approximately 240% and 180%, respectively. The relative bioavailability of baseline adjusted total DHA was comparable for both administrations, while there was a 140% increase in AUC for baseline adjusted free DHA. Under fed conditions, unadjusted total and free EPA exposures increased by 180% and 150%, respectively, while unadjusted total and free DHA were similar for both fasted and fed conditions.

NCEP ATP III guidelines recommend that patients with severe TG elevations adhere to the lower fat Therapeutic Lifestyle Changes (TLC) diet¹. The multifaceted approach to achieving therapeutic lifestyle changes is listed in [Table 26](#) below. . Patients in the pivotal Phase 3 trial were advised to maintain a strict TLC diet for the duration of the trial. Dosing of Epanova was, however, regardless of meals.

¹ Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), located at https://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm

Table 26 Nutritional Composition of the TLC Diet

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Source: NIH Publication No. 01-3670, May 2001, Table 6, Page 21

Based on the disease condition, and the NCEP diet guidance, patients are expected to be on low-fat diet most of the time. On the rare occasion that the patients consume Epanova with a high-fat diet, it is predicted that there will be some excursions in the overall exposure of EPA, however, this is not likely to be clinically significant since the drug will be taken on a chronic basis on a predominantly low-fat diet.

2.7 Analytical

2.7.1 *Is the analytical method for EPA, DHA, R-Warfarin, S-Warfarin, Simvastatin and Simvastatin Hydroxy Acid appropriately validated?*

Over the course of the development of Epanova, three assays were used for the determination of EPA, DHA, R-Warfarin, S-Warfarin, Simvastatin and Simvastatin Hydroxy Acid concentrations in human biomatrix samples. The assays were validated for analyzing the moieties of interest in plasma samples in terms of recovery, linearity, accuracy, precision and sensitivity.

A gas chromatography plus flame ionization detector (GC/FID) assay method was developed to measure EPA and DHA, in plasma from Study SPC 275-4 in support of Omthera's development program.

In Study SPC 275-4, the content of (b) (4) EPA or DHA normalized with the total content of fatty acids (defined as the (b) (4) ranging from (b) (4)) in erythrocyte membrane was also determined separately by gas chromatography with a flame ionisation detector.

An LC/MS-MS assay was developed to measure total EPA and DHA in plasma from Study OM-EPA-001. This analysis was performed on a Micromass Quattro Ultima LC/MS/MS system, equipped with Z-Spray. The negative ions were measured in MRM mode. The analytes were quantitated using a protein precipitation-total lipid extraction/esterified fatty acids hydrolysis/liquid-liquid extraction procedure.

The concentrations of R/S-warfarin in human plasma (heparin) were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection in Study OM-EPA-006.

In Study OM-EPA-007, the concentrations of simvastatin and simvastatin hydroxy acid in human plasma were determined using high performance liquid chromatography (HPLC) with mass spectrometric detection.

A summary of key descriptive parameters for the bioanalytical assays used in clinical studies is listed in [Table 27](#).

Table 27 Summary of key descriptive parameters for EPA, DHA, R-Warfarin, S-Warfarin, Simvastatin and Simvastatin Hydroxy Acid bioanalytical assays used in clinical studies

Study Number/Report Number	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
Protocol OM-EPA-001/ Test Facility study no. AP LC/MS/MS 128.106	Analysis of Free Docosahexaenoic Acid (DHA) and Free Eicosapentaenoic Acid (EPA) in Human Plasma Using High Performance Liquid Chromatography with Tandem Mass Spectrometry (LC-MS/MS)	(b) (4)	Plasma	<u>EPA</u> 20.0 – 4000 ng/mL	<u>EPA</u> 20.0 ng/mL	<u>EPA</u> 98.5% to 101.5% at 20.0 to 4000 ng/mL	<u>EPA</u> -1.5% to 1.5% at 20.0 to 4000 ng/mL
				<u>DHA</u> 20.0 – 4000 ng/mL	<u>DHA</u> 20.0 ng/mL	<u>DHA</u> 98.7% to 101.5% at 20.0 to 4000 ng/mL	<u>DHA</u> -1.1% to 1.5% at 20.0 to 4000 ng/mL
Protocol OM-EPA-006/ Test Facility study no. AA96265-01	LC-MS/MS Determination of R/S-Warfarin in Human Plasma (Heparin)		Plasma	<u>R-Warfarin</u> 12.5 – 2500 ng/mL	<u>R-Warfarin</u> 12.5 ng/mL	<u>R-Warfarin</u> 98.6% to 101.0% at 12.5 – 2500 ng/mL	<u>R-Warfarin</u> -1.4% to 1.0% at 12.5 – 2500 ng/mL
				<u>S-Warfarin</u> 12.5 – 2500 ng/mL	<u>S-Warfarin</u> 12.5 ng/mL	<u>S-Warfarin</u> 98.9% to 100.8% at 12.5 – 2500 ng/mL	<u>S-Warfarin</u> -1.1% to 2.0% at 12.5 – 2500 ng/mL
Protocol OM-EPA-006/ Test Facility study no. 1110065.00	Analysis of Total Docosahexaenoic Acid (DHA) and Total Eicosapentaenoic Acid (EPA) In Human Plasma Using High Performance Liquid Chromatography With Tandem Mass Spectrometry (LC-MS/MS)		Plasma	<u>EPA</u> 20.0 – 4000 ng/mL	<u>EPA</u> 20.0 ng/mL	<u>EPA</u> 98.5% to 101.5% at 20.0 to 4000 ng/mL	<u>EPA</u> -1.5% to 1.5% at 20.0 to 4000 ng/mL
				<u>DHA</u> 20.0 – 4000 ng/mL	<u>DHA</u> 20.0 ng/mL	<u>DHA</u> 98.7% to 101.5% at 20.0 to 4000 ng/mL	<u>DHA</u> -1.1% to 1.5% at 20.0 to 4000 ng/mL
Protocol OM-EPA-007/ Test Facility study no. AA96264-01	LC-MS/MS Determination of Simvastatin and Simvastatin Hydroxy Acid in Human Plasma (EDTA)		Plasma	<u>Simvastatin</u> 0.100 to 20.0 ng/mL	<u>Simvastatin</u> 0.100 ng/mL	<u>Simvastatin</u> 97.8% to 104.0% at 0.100 – 20.0 ng/mL	<u>Simvastatin</u> -2.2% to 4.0% at 0.100 – 20.0 ng/mL
				<u>Simvastatin Hydroxy Acid</u> 0.100 to 20.0 ng/mL	<u>Simvastatin Hydroxy Acid</u> 0.100 ng/mL	<u>Simvastatin Hydroxy Acid</u> 98.3% to 105.0% at 0.100 – 20.0 ng/mL	<u>Simvastatin Hydroxy Acid</u> -1.7% to 5.0% at 0.100 – 20.0 ng/mL
Protocol SPC 275-4/ Test Facility study no. 15/2001 (batch 207)	Validation of a GC Assay for Quantitation of EPA and DHA in the Triglyceride Fraction of Human Plasma		Plasma	<u>EPA</u> 20.0 – 4000 ng/mL	<u>EPA</u> 1.50 µg/mL	<u>EPA</u> 99.1% to 103.2% at 30.0 to 76 µg/mL	<u>EPA</u> 2.7% to 5.9% at 11.0 to 100 µg/mL
				<u>DHA</u> 20.0 – 4000 ng/mL	<u>DHA</u> 0.70 µg/mL	<u>DHA</u> 96.4% to 101.8% at 20.0 to 36 µg/mL	<u>DHA</u> 2.0% to 5.8% at 7 to 44 µg/mL

3 Labeling Comments (Preliminary)

The following are the labeling recommendations relevant to clinical pharmacology for NDA 204961. The ~~red~~ ~~strikeout font~~ is used to show the proposed text to be deleted and underline blue font to show text to be included or comments communicated to the sponsor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)
(b) (4)
increased mitochondrial
and peroxisomal β - β -oxidation (b) (4)
(b) (4)

12.3 Pharmacokinetics

Absorption: (b) (4)
approximately 2 weeks, maximum plasma concentrations (b) (4) are achieved between 5-8 hours af (b) (4) rs after osing (b) (4) for total DHA. (b) (4)
Steady-state concentrations (b) (4) repeat daily dosing with EPANOVA (b) (4) s of

Administration of Epanova with a high-fat meal resulted in an increase in overall exposure of total and free baseline adjusted EPA by approximately 240% and 180%, respectively. There was no change in overall exposure of baseline adjusted total DHA, however, there was a 140% increase in AUC for baseline adjusted free DHA. Under fed conditions, overall exposures of unadjusted total and free EPA increased by 180% and 150%, respectively, while there was no change in overall exposure for unadjusted total and free DHA.

EPANOVA was administered without regard to meals in all clinical studies.

Distribution: Following a single 4- gram 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.

Metabolism and Excretion: EPA and DHA from EPANOVA are mainly oxidized in the liver similar to fatty acids derived from dietary sources. Following repeat dosing under low-fat meal conditions, the total apparent plasma clearance (CL/F) and half-life of baseline-adjusted EPA from EPANOVA at steady-state are 548 mL/hr and (b) (4) 37 hours, respectively. Under the same conditions, the (b) (4)

(b) (4) CL/F [and half-life of baseline-adjusted DHA are](#) (b) (4) 518 mL/hr and (b) (4) approximately 46 hours, [respectively](#). EPANOVA does not undergo renal excretion.



(b) (4)



Specific Populations

Pediatric: Pharmacokinetics of EPANOVA in pediatric patients have not been studied [see Use in Specific Populations (8.4)].

Renal or Hepatic Impairment: EPANOVA has not been studied in patients with renal or hepatic impairment.

Drug-Drug Interactions

Simvastatin: In a 14-day study of 52 healthy adult subjects, daily co-administration of simvastatin 40 mg with EPANOVA 4 grams did not affect the extent (AUC) or rate (C_{max}) of exposure to simvastatin or ^(b)₍₄₎ its major active metabolite, beta-hydroxy simvastatin at steady state.

(b) (4)

Warfarin: In a 14-day study of 52 healthy adult subjects, EPANOVA 4 grams/day at steady-state did not significantly change the single dose AUC or C_{max} of R- and S- warfarin or the anti-coagulation pharmacodynamics of 25 mg warfarin. [Frequent monitoring of INR in patients on warfarin and/or coumarin derivatives is recommended at the time of initiation or ending of Epanova treatment.](#)

In vitro studies of cytochrome P450 inhibition with EPANOVA indicated that EPANOVA administration at clinically relevant doses should not result in inhibition of CYP450 enzymes. [In vitro](#) (b) (4) -EPANOVA [did](#) (b) (4) not (b) (4) multidrug resistance associated protein (MRP) or breast cancer resistance protein (BCRP) transporters.

4 APPENDIX

4.1 OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission			
	Information		Information
NDA/BLA Number	205060	Brand Name	Epanova
OCP Division (I, II, III, IV, V)	II	Generic Name	Omevas
Medical Division	DMEP	Drug Class	Lipid altering agent
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	Adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia
OCP Team Leader	Immo Zadezensky, Ph.D.	Dosage Form	Soft gelatin capsule
Pharmacometrics Reviewer		Dosing Regimen	The (b) (4) daily dose of EPANOVA is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules). (b) (4) the daily dosage may be (b) (4) 4 grams per day, taken as a single 4-gram dose (4 capsules).
Date of Submission	07/05/2013	Route of Administration	Oral
Estimated Due Date of OCP Review	08/23/2012	Sponsor	Omthera Pharmaceuticals
Medical Division Due Date		Priority Classification	505 (b)(1) Standard
PDUFA Due Date	07/05/2014		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	3		OM-EPA-001, OM-EPA-006, OM-EPA-007
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:	X	3		STP 033/00, 03101701, 300101
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)	X	3 ^a		OM-EPA-001, OM-EPA-006, OM-EPA-007
<i>Healthy Volunteers-</i>	X	3 ^a		OM-EPA-001, OM-EPA-006, OM-EPA-007
single dose:	X	1 ^a		OM-EPA-001
multiple dose:	X	2 ^a		OM-EPA-006, OM-EPA-007
<i>Patients-</i>				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		SPC-275-4
Drug-drug interaction studies -				

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:	X	2 ^a		OM-EPA-006, OM-EPA-007
<i>in-vitro</i> :				
Subpopulation studies -				
ethnicity:				
gender:		1 ^a		Pooled analysis of healthy subject data from a single supportive Phase 1 study (SPC-275-4)
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:	X			
Phase 2:	X	1 ^a		TP0309,
Phase 3:	X	2 ^a		OM-EPA-003, OM-EPA-004
PK/PD -				
Phase 1 and/or 2, proof of concept:		2 ^a		OM-EPA-006, SPC275-4
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1		EPANOVA Clinical PK/PD Exploratory Report
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1 ^a		OM-EPA-001
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Full waiver requested
Literature References	X			
Total Number of Studies		11		

^aStudy/Studies already counted under [Healthy Volunteer Single-Dose](#) or [Healthy Volunteer Multiple-Dose](#) or [Patient Multiple-Dose](#)

^bThree (3) Phase 3 studies with PD data

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Proposed commercial formulation is the same as the one used in Phase 1, 2 and 3 studies
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Exploratory PK/PD report based on prior agreement with FDA
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The Sponsor has requested a full waiver.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please submit the bioanalytical report for Study SPC-275-4 (“A Randomized, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Multiple Ascending Oral Doses of a Highly Concentrated n-3 Polyunsaturated Fatty Acids (PUFAs) Oil derived from Fish Oil in Healthy Subjects”).

Comment to Sponsor:

Suryanarayana M. Sista

Reviewing Clinical Pharmacologist

Date

Immo Zadezensky

Team Leader/Supervisor

Date



NDA 20-5060 [505 (b)(1)] Epanova (Omefas)

Omthera Pharmaceuticals

Clinical Pharmacology Review Team:

Sury Sista

Immo Zadezensky (TL)

Background

Omefas

- Complex mixture of free polyunsaturated fatty acids (free PUFA) derived from fish oils
- Includes multiple long chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids
- Omefas contains not less than (NLT) 85% (w/w) content of free PUFA (approximately 550 mg/g EPA ; approximately 200 mg/g DHA; sum of the EPA and DHA content approximately 750 mg/g)

Advantages

- Current available therapy is 4g/day of omega-3 ethyl ester (EE) formulations required to be taken with a high-fat meal to facilitate absorption however, contraindicated in patients with hypertriglyceridemia due to impaired lipoprotein lipase activity. Ethyl esters have to undergo hydrolysis before they are bioavailable
- Epanova (omefas) provides omega-3 fatty acids in a free fatty acid (FFA) form; the bioavailability of EPA and DHA from Epanova is assumed to be near 100%, and independent of meal content.
- Lower dose (2g/day) of omefas provides greater bioavailability than standard therapy of 4g/day of omega-3 ethyl ester (EE) formulations

Overview: Clinical Pharmacology Program

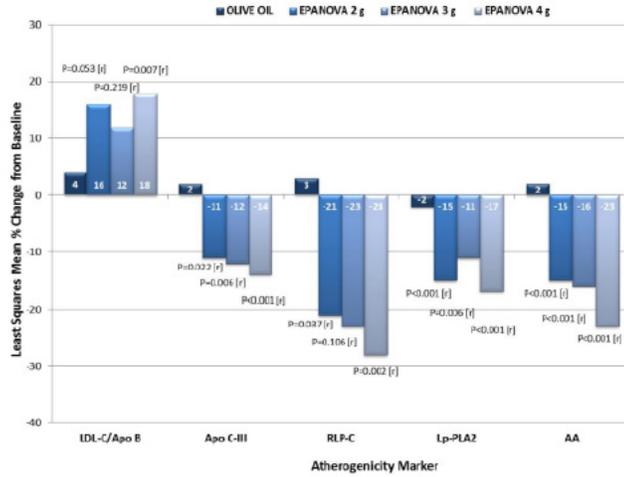
- **Clinical Pharmacology program:**
 - Pivotal Studies - 2 Phase 1, 1 Phase 2 and 2 Phase 3 studies
 - Supportive Studies – 1 Phase 1 and 1 Phase 2 studies
 - SD and MD PK Studies in Healthy Subjects, severe hypertriglyceridemic (≥ 500 and < 2000 mg/dL) subjects, and high-risk subjects with persistent hypertriglyceridemia (≥ 200 and < 500 mg/dL) despite being on statin therapy
 - Drug-Drug Interaction Studies
- **Supportive *in vitro* studies:**
 - CYP inhibition study – 2B6, 2C8 and 2C9
- **Clinical PK/PD Exploratory Report**
- **No Pivotal BE studies:**
 - Proposed commercial formulation is the same as the one used in Phase 1, 2 and 3 studies

Change in Plasma Triglyceride – EVOLVE Trial

Table 11.4.1 Baseline and % Change from Baseline to End of Treatment in Serum Triglycerides — MITT and MPP Populations

Triglycerides	Olive Oil (N=99)	Epanova		
		2 g (N=100)	3 g (N=101)	4 g (N=99)
MITT Population				
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]

Sponsor's Dose Selection Rationale



Phase 3 Study – OM-EPA-003 (EVOLVE)

- Less differentiated efficacy of the 3 g/day versus the 2 g/day dose
- Facilitating dose selection across the indications for severe hypertriglyceridemia (TG ≥500 mg/dL) and persistent hypertriglyceridemia (≥200 and <500 mg/dL while on a statin).
- The 2 and 4 g/day EPANOVA recommendation will make the dosage and administration guidance more straightforward for both physicians and patients, and the available dosages will be consistent across the hypertriglyceridemia indications.

Overview: PK & PD

- **Pharmacokinetics**
 - Linear pharmacokinetics between 2 g and 8 g doses
 - Median T_{max} - EPA: ~ 4.5 – 5.5 h; DHA: 4.7 – 5.3 hrs
 - $T_{1/2}$ – EPA: 4.7 – 10.8 h; DHA: ~7 h
 - Mean EPA and DHA trough levels similar at 16 and 52 weeks of daily dosing of 4 g Epanova
 - approximate 2-fold accumulation of EPA during continued dosing
 - Effect of race on the PK of EPA and DHA not studied
- **Pharmacodynamic Effects**
 - Following oral administration, Epanova (omefas) :
 - decreases the erythrocyte membrane concentration of arachidonic acid (AA) and increases concentrations of EPA and DHA in the erythrocytes
 - decrease serum triglyceride (TG) levels
- **QT**
 - Per agreement from the Agency (letter dated 03Oct2012), in lieu of conducting a thorough QTc study, ECGs were collected during the Phase 3 study (EVOLVE) and evaluated

Major Clin Pharm Studies

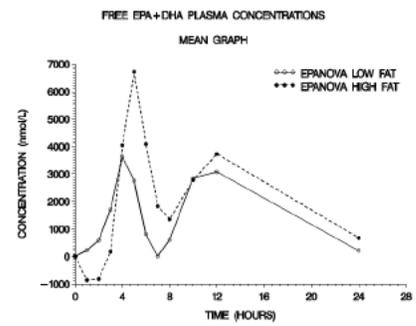
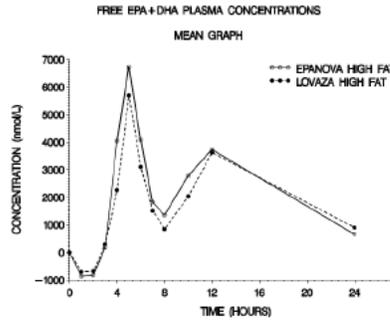
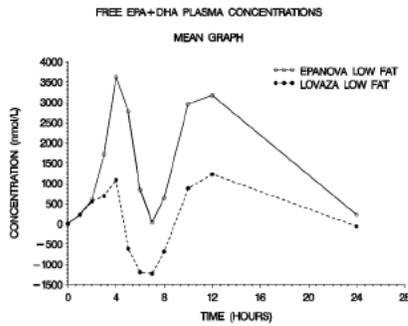
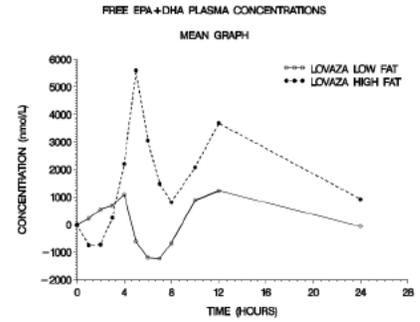
- 1. Relative Bioavailability of A Single Dose of Epanova vs. Lovaza After a Low-Fat and High-Fat Meal [Study OM-EPA-001]

- Design:

- Single-dose, randomized, open-label, 4-way XO;
- 7-day washout between treatments

- Comparisons:

- 1. Epanova low-fat versus Lovaza low-fat
- 2. Epanova high-fat versus Lovaza high-fat
- 3. Epanova high-fat versus Epanova low-fat
- 4. Lovaza high-fat versus Lovaza low-fat.



OM-EPA-001 Conclusions

- Epanova has a 4-fold greater bioavailability relative to Lovaza[®] during a low-fat diet
- Overall systemic exposure of EPA and DHA appeared to decrease by approximately 15% for Epanova when changing from a high-fat to low-fat diet. For Lovaza, there was a 5-fold difference in AUC for free EPA and DHA between the high-fat vs. low-fat diet

Major Clin Pharm Studies

- 2. MD Epanova on SD Warfarin, and MD Epanova vs. MD Lovaza [Study OM-EPA-006]
 - Design:
 - Cohort 1: Open-label, 2 treatment, 1-sequence; MD Epanova on PK and PD of SD warfarin
 - Cohort 2: Open-label, 1 treatment MD Lovaza;
 - Comparisons:
 - 1. Epanova on the PK and PD of a single 25 mg dose of warfarin
 - 2. Epanova vs. Lovaza (Total EPA, Total DHA, and Total EPA+DHA)

Figure 1 Mean (SD) Plasma R-warfarin Concentrations – Semi-Log Scale

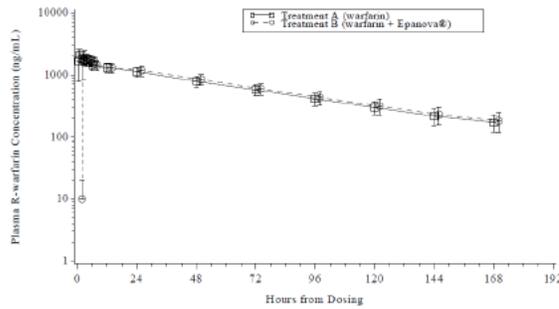


Figure 3 Mean (SD) Plasma S-warfarin Concentrations – Semi-Log Scale

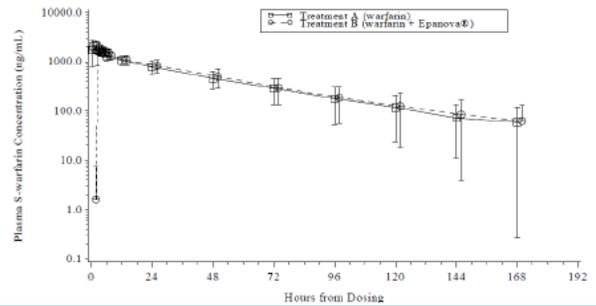


Figure 5 Mean (SD) Warfarin PT INR – Linear Scale

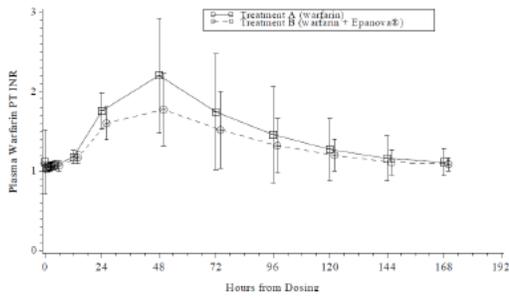


Figure 8 Mean (SD) Baseline-Adjusted Plasma Total EPA Concentrations Semi-Log Scale

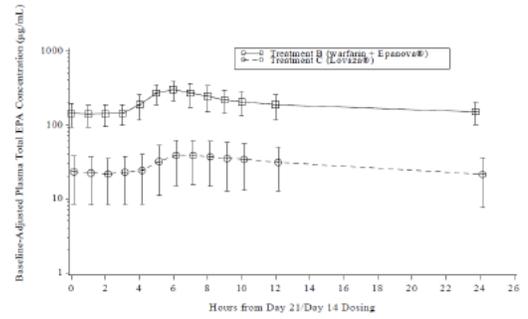


Figure 12 Mean (SD) Baseline-Adjusted Plasma Total DHA Concentrations Semi-Log Scale

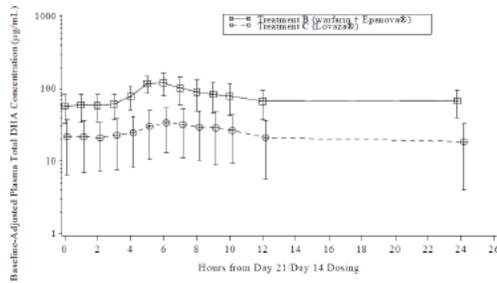
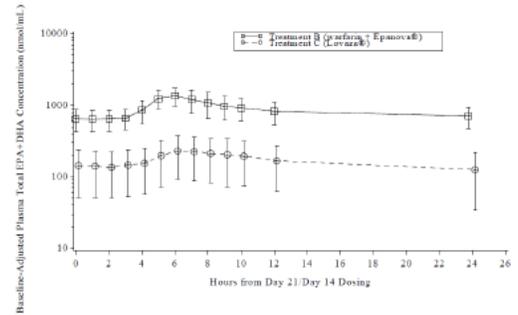


Figure 16 Mean (SD) Baseline-Adjusted Plasma Total EPA+DHA Concentrations Semi-Log Scale



OM-EPA-006 Conclusions

- Once-daily 4 g doses of Epanova® for 21 days had no effect on the PK and PD of a single 25 mg dose of warfarin
- Overall exposure ($AUC_{0-\tau}$) to baseline-adjusted Total EPA, Total DHA, and Total EPA+DHA, was approximately 7-, 3-, and 6-fold higher, respectively, with Epanova than with Lovaza

Major Clin Pharm Studies

- 3. MD Epanova on MD Simvastatin [Study OM-EPA-007]
 - Design:
 - Open-label, 2-WXO, MD Epanova and MD Simvastatin in one period and MD simvastatin in another period
 - Comparisons:
 - 1. Epanova on the PK of simvastatin
 - 2. Correlate platelet reactivity and aspirin resistance with circulating levels of fatty acids (EPA, DHA, AA, EPA+DHA and the ratio of EPA to AA [EPA:AA]), and identify potential gene polymorphisms involved in the response)

Figure 1 Mean (SD) Plasma Simvastatin Concentrations – Semi-Log Scale

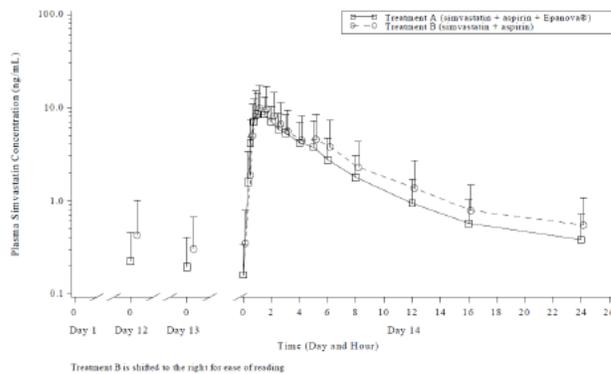
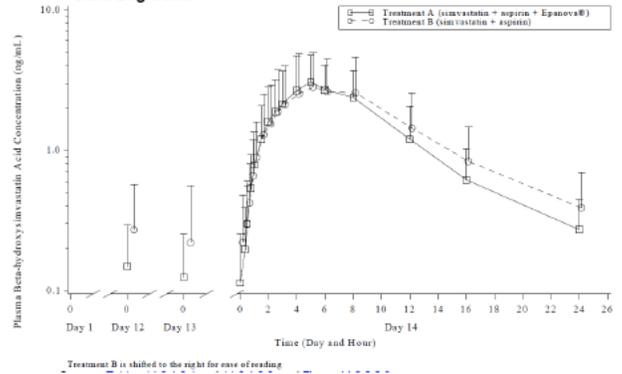


Figure 3 Mean (SD) Plasma Beta-hydroxysimvastatin Acid Concentrations – Semi-Log Scale



OM-EPA-007 Conclusions

- Once-daily, 4-g doses of Epanova® for 14 days had no effect on the PK of simvastatin and β -OH simvastatin acid following once-daily administration of 40 mg simvastatin and 81 mg aspirin for 14 days
- Concomitant multiple-dose administration of Epanova did not appear to alter the anti-platelet activity of low-dose aspirin.

Overview: Extrinsic/Intrinsic Factors

- **Drug-Drug interaction:** No dose adjustment for warfarin, simvastatin, and aspirin when co-administered with Epanova
 - Concomitant administration of multiple once-daily 4 mg doses of Epanova had no impact on the PK or PD of R- or S-warfarin in plasma following the administration of a single 25 mg dose of warfarin
 - Once-daily, 4-g doses of Epanova for 14 days had no effect on the PK of simvastatin and β -OH simvastatin acid following the once-daily administration of 40 mg of simvastatin and 81 mg of aspirin for 14 days
- **Renal Impairment :** Not studied
- **Hepatic Impairment:** Not Studied
- **Effect of Gender, Age and BW:** (from supportive study SPC-275-4)
 - There was no apparent effect of gender on the pharmacokinetics of EPA or DHA.
 - There appear to be positive relationships between EPA C_{max} (Day 43) and AUC (Days 1 and 43) and age.

Pediatric Plan

- **Sponsor Request**
 - Full waiver of the requirement for studies of pediatric use of Epanova according to 21CFR 315.55(b). The waiver was requested for all pediatric age groups.

Key Questions: Mid Cycle Deliverables

- Is the food-effect (clinical experience, and low-fat/high-fat comparison to lovaza) sufficient?
- What is the exposure-efficacy relationship?
- Were there any bleeding events?
- Is there any need for dose adjustment based on intrinsic factors?
- Is there any need for dose adjustment based on extrinsic factors?



Information Requested

- Bioanalytical report for Study SPC-275-4

Conclusions

- This NDA is filable from OCP perspective
- No OSI inspection is requested

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

/s/

SURYNARAYANA M SISTA
03/26/2014

IMMO ZADEZENSKY
03/27/2014

BIOPHARMACEUTICS REVIEW			
Office of New Drug Quality Assessment			
Application No.:	NDA 205-060	Reviewer:	
Division:	DMEP	Houda Mahayni, Ph.D.	
Applicant:	Omthera Pharmaceuticals, Inc.	Team Leader:	
Trade Name:	Epanova™	Angelica Dorantes, Ph.D.	
Generic Name:	omega-3 carboxylic acid (Omevas)	Acting Supervisor:	
Indication:	As adjunct to diet to reduce triglyceride levels in adult patient with severe hypertriglyceridemia (≥ 500 mg/dL)	Date Assigned:	July 10, 2013
Formulation/strength	Coated Soft Gelatin Capsule/1000 mg	Date of Review:	March 24, 2014
Route of Administration	Oral		
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission Dates		GRMP Date	PDUFA Date
July 5, 2013 January 3, 2014		March 27, 2014	May 5, 2014
Type of Submission:	505 (b) (1)		
Key review points	<ol style="list-style-type: none"> 1. Dissolution method and acceptance criteria 2. Data supporting the acceptability of immediate release designation 3. The acceptability of comparability protocol for the drug product manufacturing site change 		

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14. What is the composition of the formulation of the proposed product?
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16. Are all the strengths evaluated in the pivotal clinical trials? If not, what data are available to support the approval of lower strengths?

17. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

18. Is the formulation of the clinical product the same formulation of the to-be-marketed product? If not, what information is available to support the formulation changes?

19. Is the manufacturing site the same for the clinical and to-be-marketed products? If not, what information is available to support the new site?

**D) DISSOLUTION APPLICATIONS 43
D.1 BIOWAIVERS**

20. Is there a waiver request of in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

D) SUMMARY OF BIOPHARMACEUTICS FINDINGS

The NDA is a 505 (b) (1) application for Omefas, a complex drug substance consisting of a mixture of polyunsaturated free fatty acids (PUFAs) that is derived from fish oils. The drug product is a coated soft gelatin capsule containing 1,000 mg of drug substance (Omefas). The proposed indication is lowering serum triglyceride levels.

The film coat used is (b) (4) polymer which is an (b) (4) dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate and does not exhibit enteric release characteristics. According to the Applicant, Epanova capsules utilize the properties of (b) (4) in a (b) (4) application in which the capsules are coated with (b) (4). In an aqueous environment, (b) (4) the coating and the gelatin shell resulting in a (b) (4) capsule rupture. According to the Applicant, this polymer produces the (b) (4) capsule rupture that is (b) (4).

The manufacturing process of Epanova drug product is composed of (b) (4) steps:
(b) (4)

This review focuses on the evaluation of: 1) Dissolution method and acceptance criteria, 2) Data supporting the acceptability of immediate release designation, and 3) The acceptability of comparability protocol for the drug product manufacturing site change.

1) Dissolution Method and Acceptance Criteria:

The following dissolution method and acceptance criteria for Omefas Capsules, 1000 mg were proposed by the Applicant:

USP Apparatus	Paddle Rotation	Medium Volume	Temperature	Medium	Acceptance Criteria
II with a sinker device incorporating a mass	50 rpm	900mL	37°C	pH 5.5 Phthalate buffer containing 2% SDS	NMT (b) (4) % release after 30 minutes, and Q = (b) (4) % after 120 minutes

The proposed dissolution method and acceptance criteria are acceptable. It is possible that an (b) (4) time point than the proposed 120 minutes may be more suitable (i.e., (b) (4) minutes) as an acceptance time limit. However, the Applicant did not provide full dissolution profile for stability batches, so it is not possible to determine if an (b) (4) time point is suitable. The discriminating ability of the dissolution method is lacking due to the high variability of the method. FDA raised the dissolution method variability with the Applicant during the Type C meeting held on November 6, 2013. The Applicant provided data on January 3, 2014 which demonstrated that the variability of the dissolution method has no impact on the in-vivo performance of the product.

2) Data supporting the acceptability of immediate release designation:

FDA sent the Applicant a Filing Communication – Filing Review Issues Identified letter dated September 16, 2013. Among other issues identified, Biopharmaceutics expressed its concern with the dosage form designation as (b) (4)

(b) (4)

FDA granted the meeting which was held on November 6, 2013. At the meeting, the Applicant provided information to show that the coating in Epanova capsules is (b) (4), and the bioavailability of Epanova is comparable to Lovaza (uncoated capsule), as the T_{max} of both products are similar and the shape of the mean plasma concentration-time profiles for Epanova (coated-capsule) and Lovaza (uncoated capsule) are similar. Based on the additional information provided at the meeting, FDA agreed with the immediate-release designation for the product. (For more information, refer to Meeting Minutes in DARRTS dated January 23, 2014)

3) The acceptability of comparability protocol for the drug product (b) (4)

Presently, the Applicant's contractor is Catalent located in Germany. It manufactures the finished bulk drug product. The (b) (4) operations are performed at Catalent (Eberbach site, formerly known as (b) (4)) while the (b) (4) operations are performed at the Catalent (Schornforf site). The Applicant intends to (b) (4)

(b) (4)

For dissolution documentation, the Applicant plans to (b) (4). FDA found the Applicant's plans acceptable.

II) RECOMMENDATION

ONDQA-Biopharmaceutics had reviewed NDA 205-060 for Epanova (Omefas) capsules, 1000 mg.

The following dissolution method and dissolution acceptance criteria are acceptable.

USP Apparatus	Paddle Rotation	Medium Volume	Temperature	Medium	Acceptance Criteria
II with a sinker device incorporating a mass	50 rpm	900mL	37°C	pH 5.5 Phthalate buffer containing 2% SDS	NMT (b) (4)% release after 30 minutes, and Q = (b) (4)% after 120 minutes

To support the Applicant's plans to

(b) (4)

are acceptable.

From the Biopharmaceutics perspective, NDA 205-060 for Epanova (Omevas) Capsules is recommended for APPROVAL.

Houda Mahayni, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) BIOPHARMACEUTICS ASSESSMENT-QUESTION BASED REVIEW APPROACH

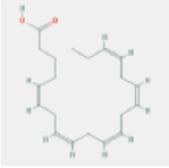
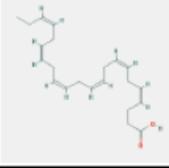
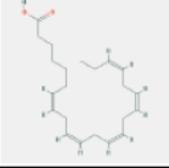
A) GENERAL ATTRIBUTES

1. What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?

Omefas is a complex drug substance consisting of a mixture of polyunsaturated free fatty acids (PUFAs) that is derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant form of omega-3 fatty acids.

Table 1 shows structure summaries for the three most abundant Omega-3 fatty acids contained in Omefas.

Table 1: Structure Summaries for the Three Most Abundant Omega-3 Fatty Acids Contained in Omefas

Attribute		
EPA	Molecular Formula	$C_{20}H_{30}O_2$
	Molecular Weight	302.451 g/mol
	Amount contained in omefas	500 to 600 mg/g
	Structure	
DHA	Molecular Formula	$C_{22}H_{32}O_2$
	Molecular Weight	328.488 g/mol
	Amount contained in omefas	150 to 250 mg/g
	Structure	
DPA	Molecular Formula	$C_{22}H_{34}O_2$
	Molecular Weight	330.504 g/mol
	Amount contained in omefas	(b) (4) mg/g
	Structure	

Omefas is a clear yellow fluid oil with a slight fish-like odor and taste. It is practically insoluble in water but highly soluble in acetone, chloroform, ethanol, ethyl acetate, diethyl ether, octanol, petroleum ether (40-60) and propylene glycol. As Omefas is insoluble in water its acidity is not measured in terms of pH. The Applicant used the acid

value (or neutralization number) to measure the amount of potassium hydroxide it takes to neutralize the carboxylic acid in the drug substance. The reported acid value for Omefas is ~ 180 mg KOH/g.

Epanova is a coated soft gelatin capsule containing Omefas and the following inactive ingredients: 3 mg α -tocopherol (in a carrier of vegetable oil), and gelatin, glycerol, sorbitol, and purified water (components of the capsule shell). The Applicant stated that the soft gelatin capsules are film-coated with poly (ethyl acrylate, methyl methacrylate),

(b) (4)
The Applicant stated that (u) (4), Epanova capsules are not enteric coated and are therefore categorized as an immediate-release dosage form.

FDA sent the Applicant a Filing Communication – Filing Review Issues Identified letter dated September 16, 2013. Among other issues identified, Biopharmaceutics expressed its concern with the dosage form designation (b) (4)

(b) (4)
The Applicant provided information to show that the coating in Epanova capsules is (b) (4), and the bioavailability of Epanova is comparable to Lovaza (uncoated capsule). The Applicant provided data to show that the T_{max} of both products are similar and the shape of the mean plasma concentration-time profiles for Epanova (coated-capsule) and Lovaza (uncoated capsule) are similar (for more information, refer Meeting Minutes in DARRTS dated January 23, 2014). Based on the information provided, FDA agreed with the immediate release designation for the product.

2. Is there any information on BCS classification? What claim did the Applicant make based on BCS classification? What data are available to support this claim?

Not Applicable, as the drug substance is an oil, and therefore is not soluble in aqueous media.

The Applicant performed solubility studies of the drug substance (Omefas) in media containing different types of surfactants (non-ionic, cationic, and anionic), and no surfactant. The Applicant found that the (b) (4) capable of dissolving Omefas using a rotation speed of (b) (4) rpm within (b) (4) minutes. The other two types of surfactants (b) (4) did not adequately solubilize Omefas.

B) DISSOLUTION INFORMATION

B.1. DISSOLUTION METHOD

3. What is the proposed dissolution method?

The Applicant stated that a drug release method for Epanova capsules was developed (b) (4)

Although the two-stage testing used in the proposed method requires sampling at two time points (30 min & 120 min), the method does not

(b) (4). As discussed in the Type C Meeting held on November 6, 2013 with the Applicant (Refer to the Meeting Minutes in DARRTS dated January 23, 2014), the coating technology utilized in Epanova capsules (b) (4)

. The proposed method parameters are listed below.

The dissolution method test parameters are:

Apparatus: UPS Type II (Paddles) with a sinker device incorporating a mass

Medium: pH 5.5 Phthalate buffer containing 2% SDS

Volume: 900 mL

Speed: 50 rpm

Temperature: 37 ± 0.5 °C

For detailed information on the dissolution method, see the attached link <\\cdsesub1\evsprod\nda205060\0000\m3\32-body-data\32p-drug-prod\epanova-capsule\32p5-contr-drug-prod\32p52-analyt-proc\op6-1083-analytical-method.pdf>.

4. What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?

The dissolution method was developed for quality control, stability testing, process development, and scale-up for manufacturing Epanova 1000 mg soft gelatin capsules.

During the development of the dissolution method, the Applicant investigated the following parameters:

- SDS concentration
- Paddle rotation speed
- pH of dissolution medium
- Mass incorporated in the sinker device

The Epanova batches used in the development of the dissolution method are shown in Table 2.

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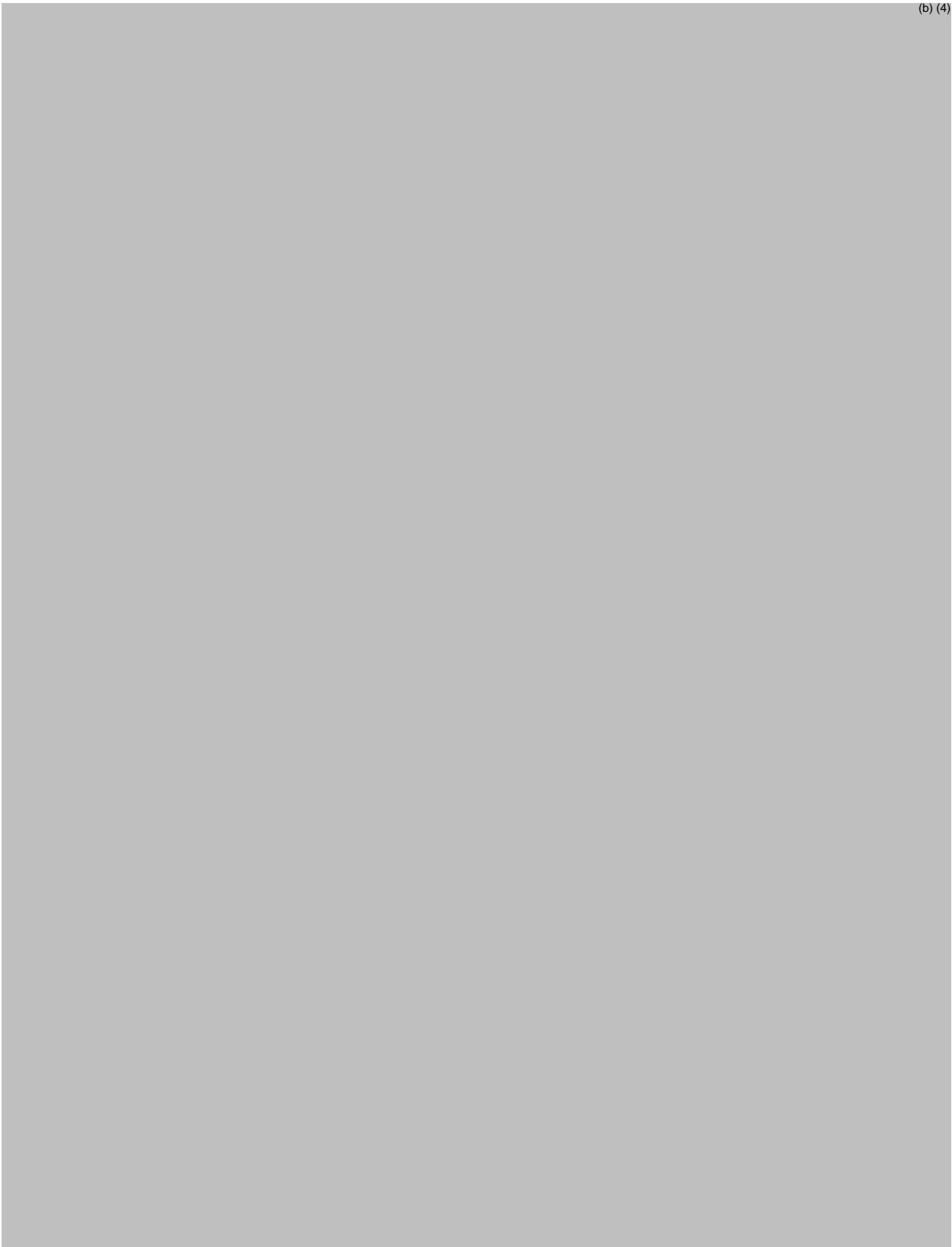
Figure 6: Omefas release profile from Epanova capsules in 2% SDS buffer pH 5.5; each line represents the mean profile from six capsules with standard deviations.



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Figure 13: Omefas release profile from Epanova capsules batch number 04X004A (solid lines) and capsules batch number 02X002A-E1 (dotted lines) in 2%SDS buffer pH 5.5; each line represents the mean profile from six capsules with standard deviations





FDA Feedback and Applicant Response

At the November 6, 2013 Type C meeting with the Applicant, FDA pointed out its concern with the high variability of the dissolution method which could result in variability in the in-vivo performance. The Applicant was asked to provide information /data on two action items from the meeting to explain/justify the observed variability and its impact on PK data.

In the submission dated January 3, 2014, the Applicant provided the following information/data (reproduced below) to each of the action items from the Type C meeting held on November 6, 2013. The first action item is to provide data in support of a lack of impact of the variability seen in the vitro dissolution method on the in vivo performance of Epanova capsule. The action items and the Applicant's responses are reproduced below.

Action Item 1: The Applicant agreed to provide 2 hour release data for the clinical lots of Epanova in 0.1 N HCl with and without 2% SDS. The Applicant and FDA agreed that the sampling should be selective not to include non-dispersed Omefas oil droplets. FDA requested that if data are being collected, a complete profile of release should be provided.

Applicant's Response:

A question from the meeting between FDA and the Sponsor on November 6, 2013 (Reference:

Sponsor's Meeting Minutes: NDA 205060 SN0009) was whether the *in vitro* variability observed in Figure 1 of the briefing document (submitted in SN0005; reproduced as Figure 1 below) could be due to an interaction of the surfactant (2% SDS) with the polymer coating. The FDA requested whether Omefas Release data was available with and without surfactant. Since this data had not been collected on the historical lots shown in Figure 1, the sponsor agreed to obtain release profiles in 0.1N HCl with and without 2% SDS for the Epanova® lots used in the clinical studies reported in the NDA.

Details for the Epanova lots used in the evaluation of Omefas release in 0.1N HCl are provided in Table 1 and experimental conditions for this modification of the Omefas Release test are provided in Table 2.

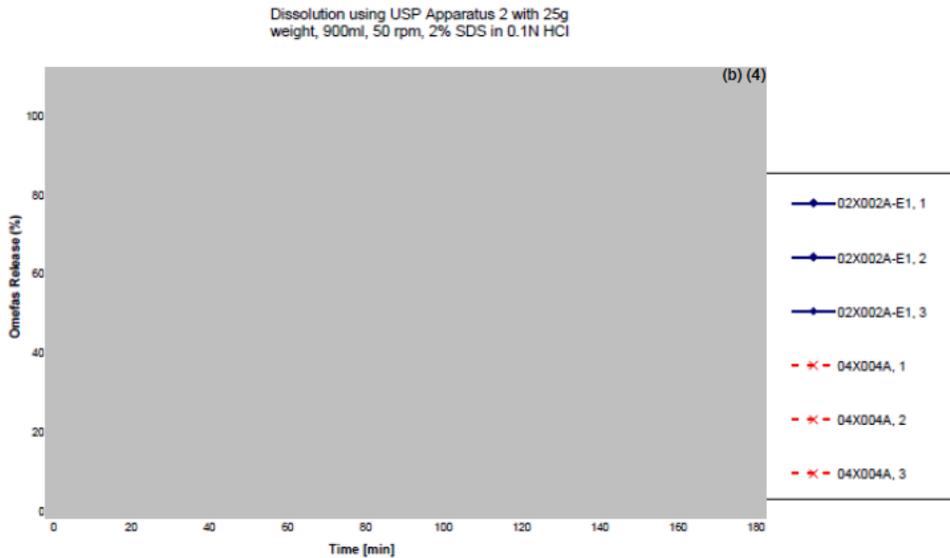


Figure 1. Omefas release profile from Epanova capsules BN04X004A (dotted lines) and BN02X002A-E1 (solid lines) in 2% SDS in 0.1N HCl. Each line represents the profile from a single capsule.

(b) (4)
(u) (4)

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Action Item 2: The Applicant agreed to provide PK data similar to the data presented in Figure 2 in the briefing document, if available, for the lots noted in Figure 1 in the briefing document or for more recent lots that are presented in the NDA.

Applicant's Response: A concern expressed by the FDA Biopharmaceutics Review team was that the variability observed in the Omefas release profiles for the two lots of Epanova capsules shown in Figure 1 of the meeting briefing document (submitted in SN0005; see reproduced Figure 1 above) could result in variability in the in vivo pharmacokinetics. The potential impact of variability in the in vitro performance of the capsules on the pharmacokinetics was discussed at the meeting and is summarized here:

- The variability in the in vitro Omefas Release profile for the two lots shown in Figure 1 is likely due to 0.1N HCl + 2 % SDS being a non-optimized media. (b) (4)
[Redacted]
- As discussed in the development report for the Omefas Release Method OP6.1083 (NDA 205060 3.2.P.2.2.3), the variability in the release profiles for the two batches shown in Figure 1 could also be attributed to (b) (4)
[Redacted]
- Variability in the Omefas Release test results obtained in 0.1N HCl does not present a safety or efficacy concern:
 - o In vivo absorption of the free fatty acids in Omefas, and the fatty acid ethyl esters in Lovaza® Capsules (following hydrolysis by pancreatic lipase) occurs exclusively in the small intestine. Fatty acids are not absorbed in the stomach.
 - o If complete release of the capsule contents occurred in the stomach, the safety profile of the coated Epanova capsules would be expected to be similar to Lovaza, which is an uncoated, immediate release soft gelatin capsule.
 - o The Omefas Release test, (b) (4)
[Redacted]

Figure 2 from the briefing document submitted in SN0005 is reproduced here as Figure 6 for easy reference; it shows the mean plasma concentration-time curve of total EPA+DHA for Epanova and uncoated Lovaza capsules and demonstrates that the t_{max} is not different for the coated Epanova capsules and the uncoated Lovaza capsules.

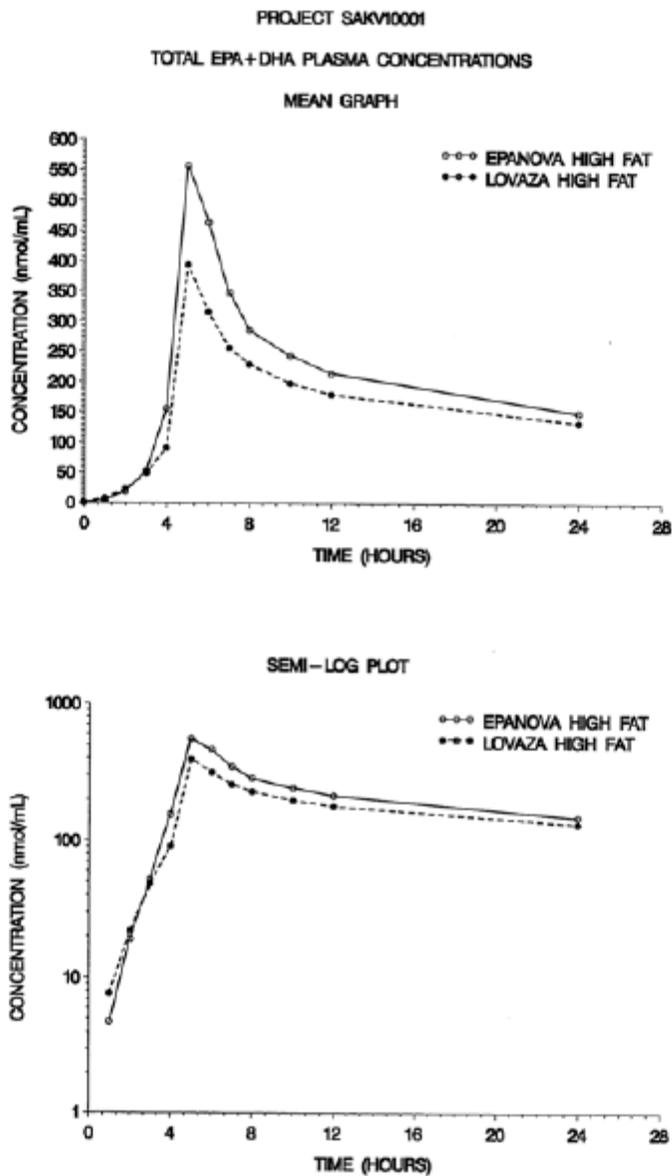


Figure 6. Total EPA + DHA plasma concentrations vs. time following administration of Epanova or Lovaza following a high fat meal. From Clinical Study Report OM-EPA-001; Section 5.3.3.1. (Originally submitted as Figure 2 in briefing document; NDA 205060 SN0005) (Epanova Batch No. 1433670001-01; Lovaza Batch Nos. OZP4551, 990757W, OZP5695, OZP6257)

Pharmacokinetic data for one of the batches shown in Figure 1 and for two more recent batches is available. Batch details and study utilization are listed in Table 3.

Table 3. Batch Utilization of Epanova in Pharmacokinetic Studies	
Batch No.	Clinical Study Utilization
02X002A-E 04X007A	EPIC-3: Study TP0309 "A One Year, Two-Center, Open-Label, Phase IIb Study of Pharmacokinetics/Pharmacodynamics, Safety and Tolerability of Epanova® Soft Gelatin Capsules 4g/day in Crohn's Disease Subjects in Remission"
1433670001-01	ECLIPSE: Study OM-EPA-001 "A Randomized, Open-Label, Four-Way Crossover Study to Compare the Relative Bioavailability of a Single Dose of Epanova® with Lovaza® After a Low-Fat and High-Fat Meal"
1442210001-09	ECLIPSE-II: Study OM-EPA-006 "An Open-Label 2-Cohort Study to Evaluate the Effect of Multiple Doses of Epanova® on the Single Dose Pharmacokinetics and Pharmacodynamics of Warfarin and to Compare the Systemic Exposure of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Following Multiple-Dose Administration of Epanova® Compared to Lovaza® in Healthy Normal Subjects"

Epanova batches 02X002A-E1 and 04X004A were used in the Omefas Release study shown in Figure 1, however Batch 04X004A was not used in any pharmacokinetic studies. Batch 02X002A-E1 was used in the EPIC-3 study which evaluated pharmacokinetics in Crohn's Disease patients. Batch 04X007A, (b) (4) Batch 04X004A, was also used in the EPIC-3 study. Figure 7 shows the EPA plasma concentration vs. time curve following 52 weeks of dosing with Epanova in the EPIC-3 trial and the corresponding in vitro Omefas Release results for batch 04X007A. Figure 8 shows the Omefas Release profiles using the validated method (pH 5.5 buffer and 2% SDS) for batches 02X002A-E1 and 04X004A and Figure 9 shows the Omefas release profile for six batches (04X004A – 04X009A) (b) (4). Although there is variability in the individual capsule release profiles, the target quality attributes of minimizing Omefas release at the 30 minute time point and achieving (b) (4) by 120 minutes are attained for all batches.

Pharmacokinetic data from two additional clinical studies (ECLIPSE and ECLIPSE-II) are presented in Figure 10 and Figure 11. Each figure shows the EPA plasma concentration vs. time curve and the corresponding in vitro Omefas Release results for the drug product batch used in the study obtained using the standard method conditions in pH 5.5 buffer containing 2% SDS. Comparing the results shown in Figure 7, Figure 10 and Figure 11 which were obtained from three separate studies using different batches of Epanova capsules, the shape of the EPA plasma concentration vs. time curves are similar. The Omefas release profiles are also similar, with some intra-batch and batch-to-batch variability observed. Figure 12 shows the Omefas release profiles (mean data), using the validated Omefas Release method, for the three batches of Epanova capsules used in the study described in Response 1. Data from Batch 04X007A was not included since the Omefas Release test was not established at the time initial testing was completed on this batch. Release profiles, at the time of initial testing, demonstrate batch-to-batch consistency.

These data suggest that any minor batch-to-batch variation in the in vitro Omefas release profiles does not influence the in vivo pharmacokinetics. Table 4 lists the observed C_{max} and t_{max} for plasma EPA from the clinical studies shown in Figure 9, Figure 11 and Figure 12. Despite the complexity of the pharmacokinetic - pharmacodynamic relationships following administration of Epanova (discussed in detail in NDA 205060 Section 5.3.4.2). Epanova Clinical PK/PD Exploratory Report), the observed t_{max} values for EPA in these three studies are consistent. This suggests that variability in Omefas release from the capsules does not affect the rate of absorption in vivo. The C_{max} values for EPA observed in these studies are significantly different and this is discussed in NDA 205060 Section 5.3.4.2. However, the variability in C_{max}, as expressed by the coefficient of variation (%CV) is similar across the three studies and is similar for Epanova and Lovaza.

Applicant's Conclusion: These data suggest that the rate and extent of absorption of the free fatty acids in Epanova capsules are not influenced by variability in Omefas release from the capsules and that the capsule coating does not increase the variability in the pharmacokinetic results.

Study	EPIC-3 ^a	ECLIPSE ^b		ECLIPSE-II ^c	
	Epanova	Epanova	Lovaza	Epanova	Lovaza
t_{max} (hr) [min – max]	5.03 [0-8.05]	5.00 [4.00-12.0]	5.00 [5.00-24.0]	6.00 [5.00-9.00]	6.56 [5.00-9.00]
C_{max} (µg/ml) [%CV]	53.23 (47.55)	133.05 (48.13)	72.88 (49.68)	295.0 (66.87)	34.22 (66.87)
Dose (g/day)	4.0	4.0	4.0	4.0	4.0
Study Drug Batch No.	02X002A-E	1433670001-01		1442210001-09	

^a EPIC-3: Study TP0309 “A One Year, Two-Center, Open-Label, Phase IIb Study of Pharmacokinetics/Pharmacodynamics, Safety and Tolerability of Epanova® Soft Gelatin Capsules 4g/day in Crohn’s Disease Subjects in Remission”. C_{max} and t_{max} values reported following 52 weeks of dosing.
^b ECLIPSE: Study OM-EPA-001 “A randomized, Open-Label, Four-Way Crossover Study to Compare the Relative Bioavailability of a Single Dose of Epanova® with Lovaza® After a Low-Fat and High-Fat Meal”. C_{max} and t_{max} values reported following a high-fat meal and a single dose to healthy normal subjects.
^c ECLIPSE-II: Study OM-EPA-006 “An Open-Label 2-Cohort Study to Evaluate the Effect of Multiple Doses of Epanova® on the Single Dose Pharmacokinetics and Pharmacodynamics of Warfarin and to Compare the Systemic Exposure of Eicosapentaenoic Acid (EPA) and Docosahexaenoic Acid (DHA) Following Multiple-Dose Administration of Epanova® Compared to Lovaza® in Healthy Normal Subjects”. C_{max} and t_{max} values reported following 15 days (Epanova) or 14 days (Lovaza) of dosing after a low-fat meal.

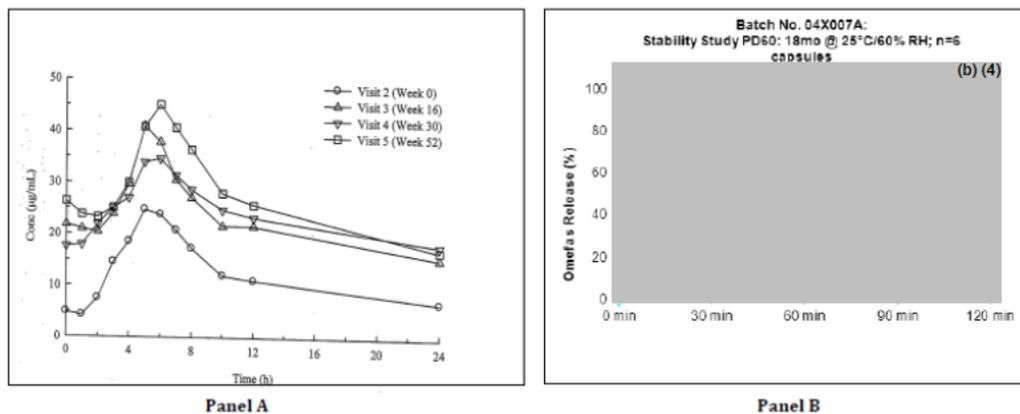


Figure 7. Panel A: Mean plasma concentrations of EPA after oral administration of Epanova 4g daily for 52 weeks to patients with Crohn’s Disease (EPIC-3 Trial, NDA 205060 Section 5.3.5.4). Panel B: Omefas Release profile for Batch No. 04X007A used in EPIC-3 Trial (from Stability Study PD60, IND 107616 SN 0000 – 3.2.P.8.1.3.1.11)

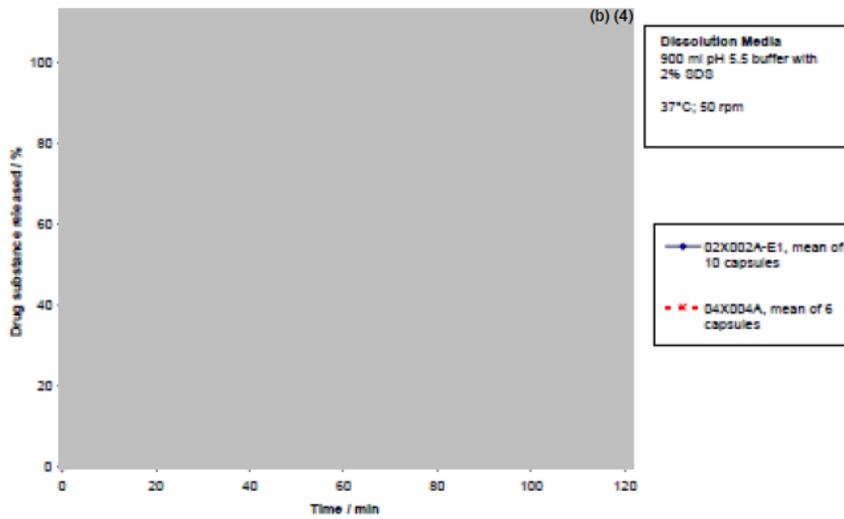


Figure 8. Omefas release profile from Epanova capsules Batch 04X004A (n=6, solid line) and Batch 02002A-E1 (n=9, dotted line); each line represents the mean profile with standard deviations. (NDA 205060 Section 3.2.P.2.2.3: Report No. 200.511)

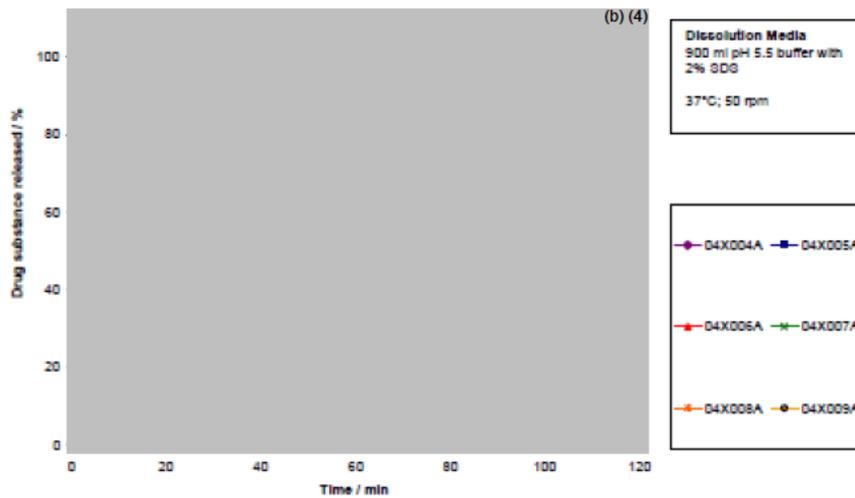
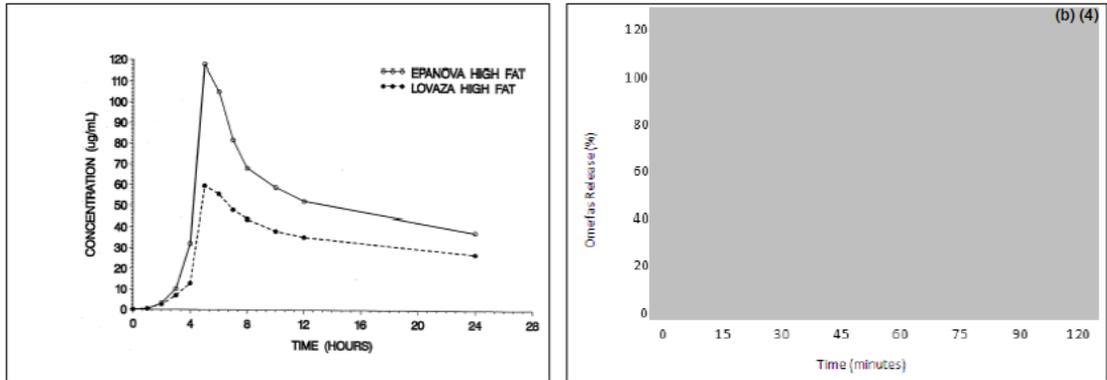


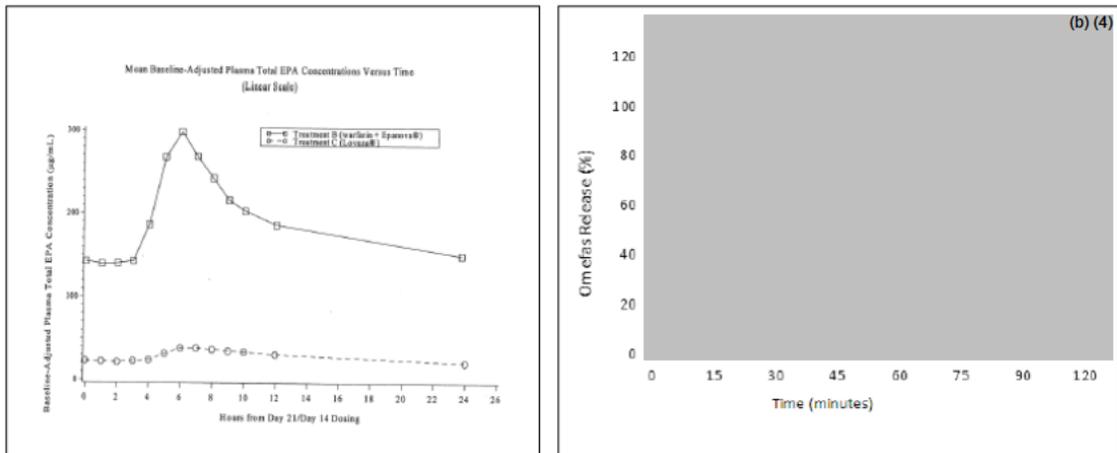
Figure 9. Omefas release profile of six Epanova batches (04X004A – 04X009A) (b)(4) Each line represents the mean profile of 6 capsules with standard deviations. (NDA 205060 Section 3.2.P.2.2.3: Report No. 200.511)



Panel A

Panel B

Figure 10. Panel A: Mean baseline corrected plasma concentrations of EPA after oral administration of a single 4g dose of Epanova or Lovaza to normal subjects following a high-fat meal (ECLIPSE Trial, NDA 205060 Section 5.3.3.1). Panel B: Omefas Release Profile for Batch No. 1433670001-01 used in ECLIPSE trial (from COA of initial results, NDA 205060 3.2.P.5.4)



Panel A

Panel B

Figure 11. Panel A: Mean baseline corrected plasma concentrations of EPA following oral administration of Epanova or Lovaza 4g daily for 14 days to normal subjects following a low-fat meal (ECLIPSE-2 Trial, NDA Section 5.3.2.2); see text for additional study details. Panel B: Omefas Release Profile for Batch No. 1442210001-09 used in ECLIPSE-2 trial (from COA of initial results; NDA 205060 3.2.P.5.4)

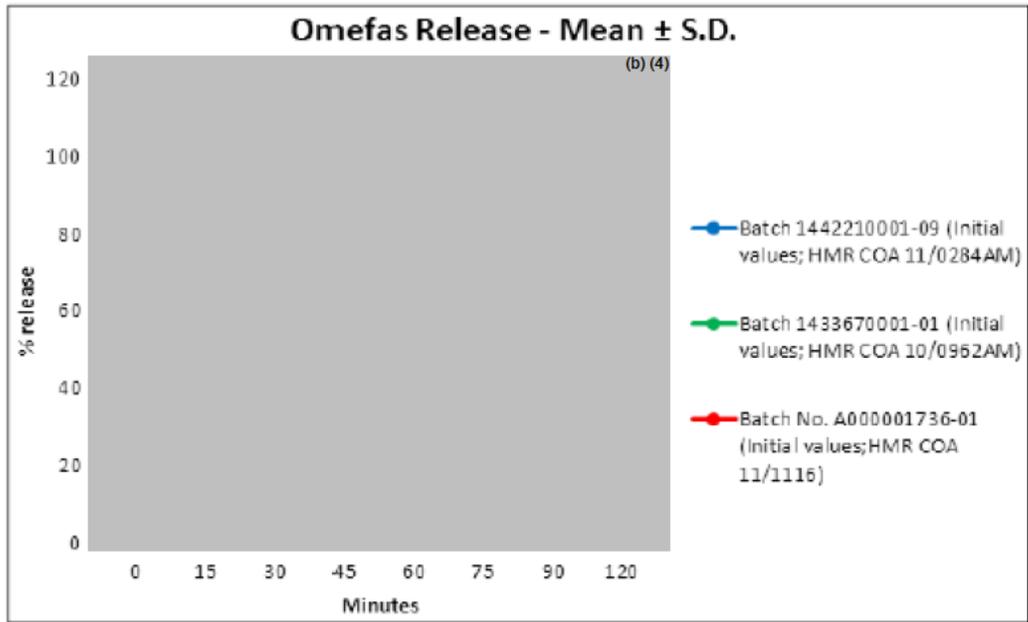


Figure 12. Omefas release for Epanova capsule Batch Nos.1442210001-09, 1433670001-01 and A000001736-01. Results are from the time of initial testing and represent the mean ± S.D. for 6 individual capsules.

Applicant's Overall Conclusion:

(b) (4)

[Redacted text]

As discussed in the Epanova Clinical PK/PD Exploratory Report (NDA 205060 Section 5.3.4.2) absorption of dietary fats and lipids, including the omega-3 fatty acids, is a complex process. Omefas release from Epanova capsules is relatively reproducible and minor variability in the in vitro release profile would not be expected to play a significant role in the in vivo performance.

Reviewer's Comment: SATISFACTORY.

The in-vitro variability is not expected to have a significant impact on the product in vivo performance.

5. What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?

According to the Applicant, Omefas contains two main active ingredients EPA (50-60%) and DHA (15-25%) and approximately (b) (4) other compounds in concentrations of (b) (4)%. The Applicant analyzed the two main active ingredients which elute at (b) (4) min (EPA) and (b) (4) min (DHA).

To quantitate the amount released, the Applicant used a reversed phase HPLC method (AM 6.1083 "Dissolution of Epanova SGC's in SDS). The quantitation range is 467

ng/mL to 2.0 mg/mL Omefas, corresponding to a range from 0.04% to 120% drug released from Epanova batches containing 15% to 25% DHA. The method is linear ($r^2 = 0.9997$), precise, and accurate over the concentration range of 1-120% Epanova batches containing 15% to 25% DHA.

Here are the links to the analytical method and validation reports:

OP6.1083 Analytical Method-Omefas Release from Epanova SGC 1000 mg.
<\\cdsesub1\evsprod\nda205060\0000\m3\32-body-data\32p-drug-prod\epanova-capsule\32p5-contr-drug-prod\32p52-analyt-proc\op6-1083-analytical-method.pdf>

Validation Report of the Analytical HPLC method (M123-Validation of the Omefas Release Test).

<\\cdsesub1\evsprod\nda205060\0000\m3\32-body-data\32p-drug-prod\epanova-capsule\32p5-contr-drug-prod\32p53-val-analyt-proc\m123-00-validation-protocol.pdf>

Validation Report M135-Validation of the Dissolution Part of AM6.1083.

<\\cdsesub1\evsprod\nda205060\0000\m3\32-body-data\32p-drug-prod\epanova-capsule\32p5-contr-drug-prod\32p53-val-analyt-proc\m135-00-validation-protocol.pdf>

Reviewer's Comment: **SATISFACTORY.**

6. What data are available to support the discriminating power of the method?

The Applicant conducted the following three assessments to evaluate the discriminatory power of the proposed dissolution method.

a. Effect of Differences in the Amount of Applied Coat

The Applicant assessed the ability of the proposed dissolution method (Paddle, 900 ml of pH 5.5 Phthalate buffer containing 2% SDS at 37°C, 25 g mass sinker device, and 50 rpm rotation speed) to discriminate between capsules prepared with different amounts of applied coat. Three sub-lots of capsules were coated (b) (4)

(b) (4)
The dissolution rate profiles are shown in Figure 16.

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Figure 19: Omefas release profile of six Epanova batches batch number 04X004A to 04X009A manufactured (b) (4); each line represents the mean profile of 6 capsules with standard deviations.



For more information on the dissolution development report see the following link:
<\\cdsesub1\evsprod\nda205060\0000\m3\32-body-data\32p-drug-prod\epanova-capsule\32p2-pharm-dev\drug-release-method-report-200-511.pdf>

Reviewer's Comment: Do not agree with the Applicant's above conclusions about the discriminating power of the method, as the inherent variability of the dissolution method is high and it is hard to discern if the results from the discriminating power of the method are not only due to the variability of the method. Note that the discriminating ability of the method also depends on the selection of the specification sampling time point(s). For some of the tested variables, the provided data indicate that (b) (4) minutes is a more adequate time point than the selected 120 minutes.

7. Is the proposed dissolution method biorelevant? What data are available to support this claim?

No, the proposed dissolution method is not biorelevant. It is intended as a quality control method.

8. Is the proposed method acceptable? If not, what are the deficiencies?

The proposed method is acceptable. Although the method variability is high and it impact its discriminating power. However, the variability does not appear to have impact in the product in vivo performance.

B.2. ACCEPTANCE CRITERIA

9. What are the proposed dissolution acceptance criteria for this product?

The proposed acceptance criteria is not more than (b) (4) % release after 30 minutes, and $Q = (b) (4) \%$ after 120 minutes. Table 3 provides the release acceptance limits after 30 minutes and after 120 minutes.

Table 3: Omefas Proposed Acceptance Criteria

Testing After 30 Minutes		
Level	Number Tested	Acceptance Criteria
A ₁	6	No individual value exceeds (b) (4) % released.
A ₂	6	The average value of the 12 units (A ₁ + A ₂) is not more than (b) (4) % released, and no individual unit is greater than (b) (4) % released.
A ₃	12	The average value of the 24 units (A ₁ + A ₂ + A ₃) is not more than (b) (4) % released, and not more than 2 individual units are greater than (b) (4) % released.
Testing After 120 Minutes		
Level	Number Tested	Acceptance Criteria $Q = (b) (4) \%$
B ₁	6	No unit is less than $Q + (b) (4) \%$.
B ₂	6	The average value of the 12 units (B ₁ + B ₂) is equal to or greater than Q; and no unit is less than $Q - (b) (4) \%$.
B ₃	12	The average value of the 24 units (B ₁ + B ₂ + B ₃) is equal to or greater than Q, not more than 2 units are less than $Q - (b) (4) \%$, and no unit is less than $Q - (b) (4) \%$.

10. What data are available to support the acceptance criteria?

The relative bioavailability study (OM-EPA-001) used Batch 1433670001-01, the Phase 3 study (EVOLVE trial, OM-EPA-003) used Batch 1442210001-C, and the registration stability batches are: 09KX19A1, 1433670001-01, 1442210001-09, and 1455620001-04.

The Applicant stated that clinical histories and long-term, intermediate and accelerated stability data support the proposed acceptance criteria. Table 4 provides the dissolution data from batches manufactured at Catalent Germany.



Table 5 and Table 6 provide the dissolution data at 30 minutes and 120 minutes at the long term, intermediate, and accelerated conditions for the market packages and clinical and physicians packages. The significant of the yellow highlighted areas in the tables below is not known.

Table 5: Percent Omefas Released at 30 minutes – Market and Clinical/Physicians Packages

(b) (4)



* = Results failing to comply with the specification criteria at level 1.

Table 6: Percent Omefas Released at 120 minutes – Market and Clinical/Physicians Packages

(b) (4)



* = Result failing to comply with level 1 and 2 criteria.

Also, Table 7 and Table 8 provide the percent Omefas released at 30 minutes and 120 minutes at the long term, intermediate, and accelerated stability conditions using coated bulk capsules. Table 9 shows the overall summary (range) of results at 30 and 120 minutes from Market, Physicians/Clinical Packages and Bulk Packages stored at the proposed long-term conditions of 25° C/60 RH.

Table 7: Omefas Release at 30 minutes- Bulk Packages

(b) (4)



* = Testing not performed due to physical damage to some capsules resulting in leakage. Tests that were considered unlikely to be affected were performed. No other samples at any other time point or storage conditions showed signs of physical damage.

Table 8: Omefas Release at 30 minutes- Bulk Packages

(b) (4)

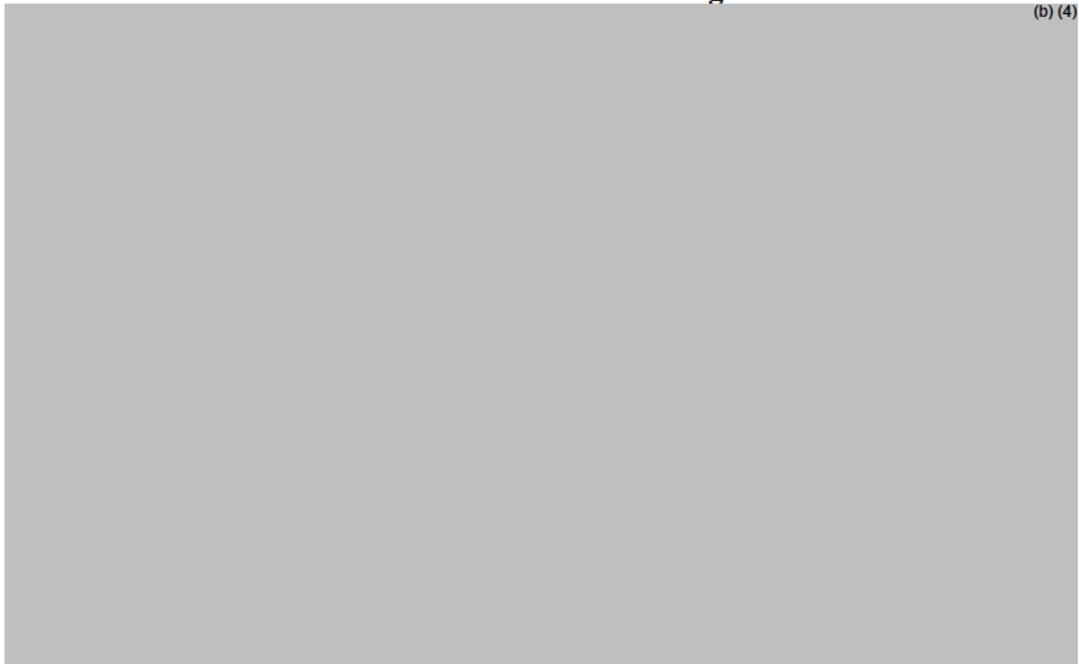


Table 9: shows the overall summary (range) of results at 30 and 120 minutes from Market, Physicians/Clinical Packages and Bulk Packages stored at the proposed long-term conditions of 25° C/60 RH.

(b) (4)

11. Is the setting of the dissolution acceptance criteria based on data from clinical and registration batches?

Yes. However, the Applicant did not provide (b) (4) profile, as the only point provided at 120 minutes time point on stability.

12. Are mean (n=12) dissolution profile data used for the setting of the acceptance criteria?

No.

13. Are the acceptance criteria acceptable? If not, what are the recommended acceptance criteria?

The overall data collected during method development, including discriminating testing indicate that the proposed criterion for the first time point at 30 minutes is appropriate and is acceptable; however for the terminal dissolution phase, the time point at which Q=(b) (4)% dissolution occurs is (b) (4) minutes instead of the proposed 120 minutes. However, based on the data provided by the Applicant demonstrating that the variability of the

dissolution data for the middle (b) (4) minutes time points and > (b) (4) % dissolution at either the (b) (4) or 120 minutes have no impact on the in-vivo performance of the product, the proposed 120 minutes acceptance criterion time point for the terminal dissolution phase is supported by these data and is also acceptable.

C) DRUG PRODUCT FORMULATION DEVELOPMENT and BRIDGING ACROSS PHASES

14. What is the composition of the formulation of the proposed product?

The components and composition of Epanova Capsules are listed in Table 10.

Table 10: Components and composition of Epanova Capsules

Ingredient	Function	Specification	Weight Per Capsule (mg)
Omefas ^a	Active ingredient	3.2.S.4.1	1,000
Capsule Shell			(b) (4)
Gelatin (porcine type A, (b) (4))	Capsule shell	USP/NF, Ph. Eur.	(b) (4)
(b) (4)			
Sorbitol (b) (4)		USP/NF, Ph. Eur.	
Glycerol (b) (4)		Ph. Eur.	
Purified Water		USP/NF, Ph. Eur.	
Total shell weight			
Capsule Coating			
Ethyl acrylate and methyl methacrylate copolymer dispersion (b) (4)	Coating polymer	NF, Ph. Eur., JP	(b) (4)
Talc		USP/NF	
Titanium dioxide		USP/NF	
Iron oxide red		USP/NF	
Polysorbate 80		USP/NF	
Carboxymethylcellulose sodium		USP/NF, Ph. Eur.	
(b) (4)		USP, Ph. Eur.	
Total coating weight			
Printing Ink ^d	Identification	USP/NF	
Total capsule weight			1,470.0
^a = (b) (4)			
^b = (b) (4)			
^c = (b) (4)			
^d = The qualitative composition of the ink is provided in Table 3.2.P.1-2			
^e = (b) (4)			

15. What are the highlights of the drug product formulation development?

The film coat used is (b) (4) polymer which is an (b) (4) dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate. According to the Applicant, the film coat does not exhibit enteric release characteristics but is (b) (4)

(b) (4). The Applicant intention from using this polymer is to (b) (4) (b) (4) Epanova capsules are not enteric coated and are therefore categorized as an immediate-release dosage form. For further discussion about the dosage form designation, see in DARRTS the meeting minutes dated 1/23/14.

16. Are all the strengths evaluated in the pivotal clinical trials? If not, what data are available to support the approval of lower strengths?

Not applicable, as only one strength (1000 mg) is proposed for marketing.

17. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

With the exception of one study, all clinical studies utilized the selected final formulation for Epanova, which is 1000 mg of Omefas (b) (4) manufactured into soft gelatin capsules that have a poly (ethyl acrylate, methyl methacrylate) coating.

18. Is the formulation of the clinical product the same formulation of the to-be-marketed product? If not, what information is available to support the formulation changes?

Yes, there are no formulation changes.

19. Is the manufacturing site the same for the clinical and to-be-marketed products? If not, what information is available to support the new site?

Presently, yes, and the present Applicant's contractor is Catalent located in Germany. It manufactures the finished bulk drug product. The (b) (4) operations are performed at Catalent (Eberbach site, formerly known as (b) (4)) while the (b) (4) operations are performed at Catalent (Schornforf site).

In the future, the Applicant plans to (b) (4) (b) (4)

(b) (4) The Applicant submitted a comparability protocol describing its plan for the (b) (4) (b) (4). Table 11 describes the current and proposed drug product (b) (4)

Table 11: (b) (4) **Drug Product Manufacturing Sites**

The Applicant plans to report and submit to the NDA using the reporting category Changes Being Effected-30 supplement supportive test data and product manufacturing information to demonstrate drug product equivalency. (b) (4)

(b) (4)

(b) (4)

Reviewer's Comment: SATISFACTORY.

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

20. Is there a waiver request of in vivo BA or BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s? Is the biowaiver request acceptable?

Not applicable, as only one strength (1000 mg) is proposed for marketing.

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/s/

HOUDA MAHAYNI
03/26/2014

ANGELICA DORANTES
03/26/2014

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

NDA Number	205-060
Submission Date	July 5, 2013
Product name, generic name of the active	Epanova™ (omefas)
Dosage form and strength	Coated Soft Gelatin Capsule
Indication	As adjunct to diet to reduce triglyceride levels in adult patient with severe hypertriglyceridemia (≥ 500 mg/dL)
Applicant	Omthera Pharmaceuticals, Inc.
Clinical Division	DMEP
Type of Submission	Original New Drug Application
Biopharmaceutics Reviewer	Houda Mahayni, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

I. SUBMISSION OVERVIEW

NDA 205060 was submitted in accordance with Section 505(b) (1) of the FDC Act and 21 CFR 314.50 for use of Epanova™ (omefas) capsules as adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL). Epanova will be administered orally in 1000 mg soft gelatin capsules (b) (4)

The mechanisms by which omega-3 fatty acid treatment lowers TG levels are believed to primarily involve a reduction in hepatic TG secretion and enhanced rate of TG hydrolysis and clearance from the circulation. The Applicant stated that Epanova overcome the following limitations of the current omega-3 therapy for this indication using omega-3 ethyl ester (EE) formulations (Lovaza® and Vascepa®):

- the fixed doses available (4 grams/day)
- the optimal absorption of omega-3 ethyl ester (EE) formulations requires the medication be taken with a high fat meal which is contraindicated in patients with hypertriglyceridemia due to impaired lipoprotein lipase activity which potentially could result in more severe postprandial hypertriglyceridemia

The Applicant stated that Epanova™ (omefas) is the first formulation to provide omega-3 fatty acids in a free fatty acid (FFA) chemical structure. Because the omega-3 fatty acids in Epanova are provided as FFAs, the bioavailability of EPA and DHA from Epanova is assumed to be near 100%, and independent of meal content. The Applicant reported that the increased bioavailability of Epanova allows using an efficacious starting dose of 2 grams/day instead of the 4 grams/day used with other approved omega-3 ethyl ester (EE) formulations such as Lovaza and Vascepa.

The clinical package of the NDA for the indication of Epanova as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia includes one pivotal clinical trial (*Protocol OM-EPA-003*; EVOLVE), three pharmacokinetic studies (*OM-EPA-001*, *SPC-275-4*, *EPIC-3*) and two drug interaction studies with warfarin and simvastatin (*OM-EPA-006* and *OM-EPA-007*, respectively).

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II. BIOPHARMACEUTICS SUMMARY INFORMATION

Omefas is a complex drug substance consisting of a mixture of polyunsaturated free fatty acids (PUFAs) that is derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant form of omega-3 fatty acids.

Omefas is a clear yellow fluid oil with a slight fish-like odor and taste and is practically insoluble in water but highly soluble in acetone, chloroform, ethanol, ethyl acetate, diethyl ether, octanol, petroleum ether (40-60) and propylene glycol. As omefas is insoluble in water its acidity is not measured in terms of pH. Alternatively, acid value (or neutralization number) is used to measure the amount of potassium hydroxide it takes to neutralize the carboxylic acid in the drug substance. The acid value for omefas is ~ (b) (4) mg KOH/g.

The Applicant stated that drug substance is absorbed by a complex process involving the

(b) (4)

Epanova is a coated soft gelatin capsule containing a complex mixture of free polyunsaturated fatty acids (free PUFA) derived from fish oils (omefas), including multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids. Epanova capsules also contain the following inactive ingredients: 3 mg α -tocopherol (in a carrier of vegetable oil), and gelatin, glycerol, sorbitol, and purified water (components of the capsule shell). The soft gelatin capsules are film-coated with poly (ethyl acrylate, methyl methacrylate), a (b) (4)

The Applicant stated that although there is (b) (4), Epanova capsules are not enteric coated and are therefore categorized as an immediate-release dosage form. According to the Applicant, with the exception of the (b) (4) characteristics, there are no physicochemical and biological properties relevant to the performance of the finished product. The (b) (4) coating is applied (b) (4).

The manufacturing process for Epanova drug product is performed in (b) (4) discrete steps –

(b) (4)

The final drug product container closure system is a commercially available white opaque high-

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

density polyethylene bottle with a _____ white opaque _____ screw cap. b(4)

The components and composition of Epanova capsules are listed in Table 1.

Table 1: Drug Product Composition

Ingredient	Function	Specification	Weight Per Capsule (mg)
Omefas ^a	Active ingredient	3.2.S.4.1	1.000
Capsule Shell			
Gelatin (porcine type A, _____)	Capsule shell	USP/NF, Ph. Eur.	_____
Sorbitol: _____		USP/NF, Ph. Eur.	_____
Glycerol: _____		Ph. Eur.	_____
Purified Water		USP/NF, Ph. Eur.	_____
Total shell weight			_____
Capsule Coating			
Ethyl acrylate and methyl methacrylate copolymer dispersion; _____		NF, Ph. Eur., JP	_____
Talc		USP/NF	_____
Titanium dioxide		USP/NF	_____
Iron oxide red		USP/NF	_____
Polysorbate 80		USP/NF	_____
Carboxymethylcellulose sodium		USP/NF, Ph. Eur.	_____
Purified water		USP, Ph. Eur.	_____
Total coating weight			_____
Printing Ink ^d	Identification	USP/NF	-
Total capsule weight			1.470.0
a = _____			
b = _____			
c = _____			
d = The qualitative composition of the ink is provided in Table 3.2.P.1-2			
e = _____			

The Applicant stated that a drug release method for Epanova capsules was developed based on the USP type 2 apparatus. The method is based on _____ utilized in Epanova capsules produces a _____ the two-stage testing used in the dissolution method requires sampling at two time points (30 min & 120 min) to capture the requirements for capsule rupture test, _____ b(4)

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The Applicant stated that all clinical studies which were performed in support of the current application utilized the selected final formulation for Epanova.

III. RECOMMENDATION:

The Biopharmaceutics review will evaluate the acceptability of the dissolution method, acceptance criteria, and comparability protocol for the drug product (b) (4). The following comments and requests for information should be conveyed to the Applicant in the 74-Day letter.

1. We do not agree with your “**Immediate Release**” claim for your proposed drug product. (b) (4)

(b) (4)

(b) (4)

Therefore, revise the dissolution method as appropriate by implementing an “**Acid Stage**” followed by a “**Buffer Stage**” testing.

3. Also, revise the dissolution acceptance criteria as appropriate and provide your proposal and the supportive data. (b) (4)

You should use the dissolution profile data from the bio-batches (PK and clinical) and stability-registration batches to set the acceptance criteria.

- **Acid Stage:** No individual tablet exceeds (b) (4)% dissolved at 2 hours.

- **Buffer Stage:** The dissolution acceptance criteria for your product should be based on the following:

- o The in vitro dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
- o The selection of the specification time point should be where $Q = (b) (4)\%$ dissolution occurs. However, if you have a slowly dissolving product in the buffer stage, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q = (b) (4)\%$ dissolution occurs.
- o The dissolution acceptance criterion should be based on average in vitro dissolution data (n=12).

4. (b) (4)

(b) (4)

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(b) (4)

5. As per SUPAC-MR Level 3, data from a bioequivalence study are needed to support the approval of the proposed (b) (4) for your (b) (4) product. Revise the drug product (b) (4) comparability protocol as appropriate to include this assessment.
6. Provide additional stability data using the revised dissolution method.

Although some information is lacking, overall it is a review issue and therefore from the Biopharmaceutics perspective NDA 205-060 for Epanova™ (omefas) Soft Gelatine Capsules is fileable.

IV. POTENTIAL REVIEW ISSUES – DAY 74 LETTER COMMENTS

The following parameters for the ONDQA’s Product Quality - Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

ONDQA-BIOPHARMACEUTICS				
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING				
	Parameter	Yes	No	Comment
1.	Does the application contain dissolution data?	x		
2.	Is the dissolution test part of the DP specifications?	x		The proposed dissolution test parameters are: <ul style="list-style-type: none"> • USP Apparatus 2 • Dissolution medium – 900ml of pH 5.5 phthalate buffer containing 2% SDS at 37°C. • Applied mass of 25g in a specially designed sinker device (a sinker device incorporating a mass that is applied to the capsule to ensure complete release of Omefas). • Stirrer speed 50 rpm
3.	Does the application contain the dissolution method development report?	x		
4.	Is there a validation package for the analytical method and dissolution methodology?	x		

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5.	Does the application include a biowaiver request?		x	
6.	Does the application include an IVIVC model?		x	
7.	<p>Is there a modified-release claim? If yes, address the following:</p> <p>a) Is there information submitted to support the claim in accordance with 320.25 (f)?</p> <p>b) Is there information on the potential for alcohol-induced dose dumping?</p>		x	<p>The Applicant claims that the capsule is an immediate release dosage form. (b) (4) the coating applied (poly (ethyl acrylate, methyl methacrylate) polymer was used to achieve (b) (4) by 120 minutes.</p> <p>The proposed acceptance criteria: <u>At 30 minutes:</u> No individual value exceeds (b) (4)% released at S1 level. Average of 12 units is NMT (b) (4)% released and no unit is greater than (b) (4)% released at S2 level. Average of 24 units is NMT (b) (4)% released and NMT 2 individual units exceed (b) (4)% released at S3 level <u>AT 120 minutes:</u> No unit is less than $Q + \frac{(b)(4)}{(4)}\%$ (where $Q = \frac{(b)(4)}{(4)}\%$) at S1 level. Average of 12 units is equal or greater than Q and no unit is $< Q - \frac{(b)(4)}{(4)}\%$ at S2 level. Average of 24 units is equal or greater than Q and NMT 2 units are $< Q - \frac{(b)(4)}{(4)}\%$ and no unit is $< Q - \frac{(b)(4)}{(4)}\%$ at S3 level</p>
8.	Is information such as BCS classification mentioned, and supportive data provided?		x	Not applicable.
9.	Is information on mixing the product with foods or liquids included?		x	Not applicable.
10.	Is there any in vivo BA or BE information in the submission?	x		A randomized, open-label, four-way crossover study to compare the relative bioavailability of a single dose of Epanova® With Lovaza® after a low-fat and high-fat meal
11.	Is there any design space proposed using in vitro release as a response variable?		X	
12.	Is the control strategy related to in vitro drug release?		X	Not applicable.
13.	Is there any comparability protocol?	x		To support a manufacturing site change.

PRODUCT QUALITY - BIOPHARMACEUTICS FILING REVIEW

B. FILING CONCLUSION				
	Parameter	Yes	No	Comment
14.	IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	x		<ul style="list-style-type: none"> The NDA is fileable from Biopharmaceutics Perspective. The acceptability of the dissolution method, acceptance criteria, and comparability protocol are review issues.
15.	<i>If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.</i>			<i>Not Applicable.</i>
16.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?	x		<ul style="list-style-type: none"> There are six Biopharmaceutics comments and requests for information in page 4 and 5 of this filing review that need to be conveyed to the Applicant in the 74-Day letter.

{See appended electronic signature page}

Houda Mahayni, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

Date

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

/s/

HOUDA MAHAYNI
09/10/2013

ANGELICA DORANTES
09/10/2013

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	205060	Brand Name	Epanova
OCP Division (I, II, III, IV, V)	II	Generic Name	Omefas
Medical Division	DMEP	Drug Class	Lipid altering agent
OCP Reviewer	Suryanarayana Sista, Ph.D.	Indication(s)	Adjunct to diet to reduce triglyceride (TG), (b) (4) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia
OCP Team Leader	Immo Zadezensky, Ph.D.	Dosage Form	Soft gelatin capsule
Pharmacometrics Reviewer		Dosing Regimen	(b) (4) daily dose of EPANOVA is 2 grams per day. The daily dosage should be taken as a single 2-gram dose (2 capsules). (b) (4) the daily dosage may be (b) (4) taken as a single 4-gram dose (4 capsules).
Date of Submission	07/05/2013	Route of Administration	Oral
Estimated Due Date of OCP Review	08/23/2012	Sponsor	Omthera Pharmaceuticals
Medical Division Due Date		Priority Classification	505 (b)(1) Standard
PDUFA Due Date	07/05/2014		

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	3		OM-EPA-001, OM-EPA-006, OM-EPA-007
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:	X	3		STP 033/00, 03101701, 300101
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)	X	3 ^a		OM-EPA-001, OM-EPA-006, OM-EPA-007
Healthy Volunteers-	X	3 ^a		OM-EPA-001, OM-EPA-006, OM-EPA-007
single dose:	X	1 ^a		OM-EPA-001
multiple dose:	X	2 ^a		OM-EPA-006, OM-EPA-007

Clinical Pharmacology and Biopharmaceutics Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		SPC-275-4
Drug-drug interaction studies -				
<i>in-vivo</i> effects on primary drug:				
<i>in-vivo</i> effects of primary drug:	X	2 ^a		OM-EPA-006, OM-EPA-007
<i>in-vitro</i> :				
Subpopulation studies -				
ethnicity:				
gender:		1 ^a		Pooled analysis of healthy subject data from a single supportive Phase 1 study (SPC-275-4)
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 1:	X			
Phase 2:	X	1 ^a		TP0309,
Phase 3:	X	2 ^a		OM-EPA-003, OM-EPA-004
PK/PD -				
Phase 1 and/or 2, proof of concept:		2 ^a		OM-EPA-006, SPC275-4
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1		EPANOVA Clinical PK/PD Exploratory Report
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1 ^a		OM-EPA-001
Bio-waiver request based on BCS				Not Applicable
BCS class				Not Applicable
Dissolution study to evaluate alcohol induced dose-dumping				Not Applicable
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				Full waiver requested
Literature References	X			
Total Number of Studies		11		

^aStudy/Studies already counted under [Healthy Volunteer Single-Dose](#) or [Healthy Volunteer Multiple-Dose](#) or [Patient Multiple-Dose](#)

^bThree (3) Phase 3 studies with PD data

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Proposed commercial formulation is the same as the one used in Phase 1, 2 and 3 studies
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			Exploratory PK/PD report based on prior agreement with FDA
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	The Sponsor has requested a full waiver.
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Please submit the bioanalytical report for Study SPC-275-4 (“A Randomized, Placebo-Controlled Study of the Safety, Tolerability and Pharmacokinetics of Multiple Ascending Oral Doses of a Highly Concentrated n-3 Polyunsaturated Fatty Acids (PUFAs) Oil derived from Fish Oil in Healthy Subjects”).

Comment to Sponsor:

Suryanarayana M. Sista

Reviewing Clinical Pharmacologist

Date

Immo Zadezensky

Team Leader/Supervisor

Date



NDA 20-5060 [505 (b)(1)] Epanova (Omefas)

Omthera Pharmaceuticals

Clinical Pharmacology Review Team:

Sury Sista

Immo Zadezensky (TL)

Background

Omefas

- Complex mixture of free polyunsaturated fatty acids (free PUFA) derived from fish oils
- Includes multiple long chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA) being the most abundant forms of omega-3 fatty acids
- Omefas contains not less than (NLT) 85% (w/w) content of free PUFA (approximately 550 mg/g EPA ; approximately 200 mg/g DHA; sum of the EPA and DHA content approximately 750 mg/g)

Advantages

- Current available therapy is 4g/day of omega-3 ethyl ester (EE) formulations required to be taken with a high-fat meal to facilitate absorption however, contraindicated in patients with hypertriglyceridemia due to impaired lipoprotein lipase activity. Ethyl esters have to undergo hydrolysis before they are bioavailable
- Epanova (omefas) provides omega-3 fatty acids in a free fatty acid (FFA) form; the bioavailability of EPA and DHA from Epanova is assumed to be near 100%, and independent of meal content.
- Lower dose (2g/day) of omefas provides greater bioavailability than standard therapy of 4g/day of omega-3 ethyl ester (EE) formulations

Overview: Clinical Pharmacology Program

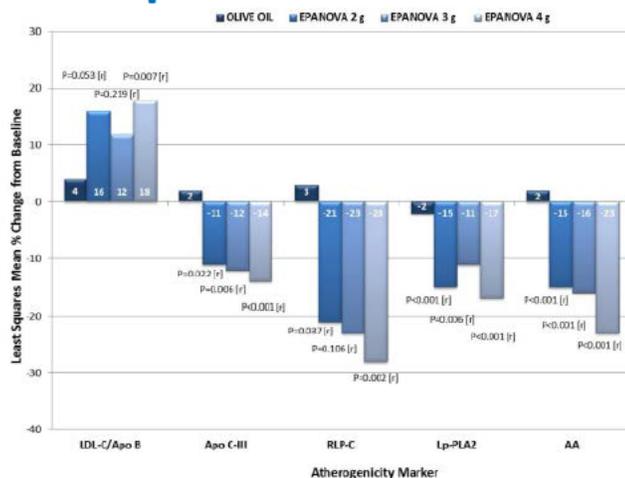
- **Clinical Pharmacology program:**
 - Pivotal Studies - 2 Phase 1, 1 Phase 2 and 2 Phase 3 studies
 - Supportive Studies – 1 Phase 1 and 1 Phase 2 studies
 - SD and MD PK Studies in Healthy Subjects, severe hypertriglyceridemic (≥ 500 and < 2000 mg/dL) subjects, and high-risk subjects with persistent hypertriglyceridemia (≥ 200 and < 500 mg/dL) despite being on statin therapy
 - Drug-Drug Interaction Studies
- **Supportive *in vitro* studies:**
 - CYP inhibition study – 2B6, 2C8 and 2C9
- **Clinical PK/PD Exploratory Report**
- **No Pivotal BE studies:**
 - Proposed commercial formulation is the same as the one used in Phase 1, 2 and 3 studies

Change in Plasma Triglyceride – EVOLVE Trial

Table 11.4.1 Baseline and % Change from Baseline to End of Treatment in Serum Triglycerides — MITT and MPP Populations

Triglycerides	Olive Oil (N=99)	Epanova		
		2 g (N=100)	3 g (N=101)	4 g (N=99)
MITT Population				
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]

Sponsor's Dose Selection Rationale



Phase 3 Study – OM-EPA-003 (EVOLVE)

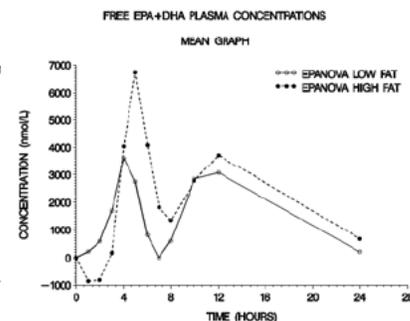
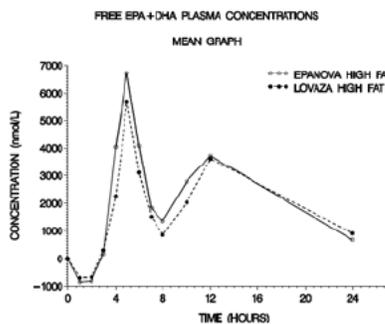
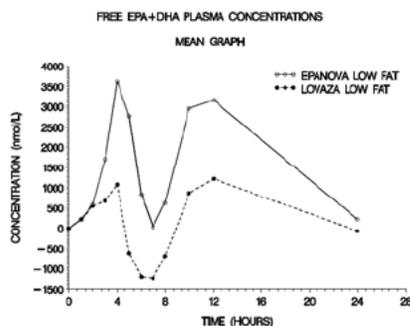
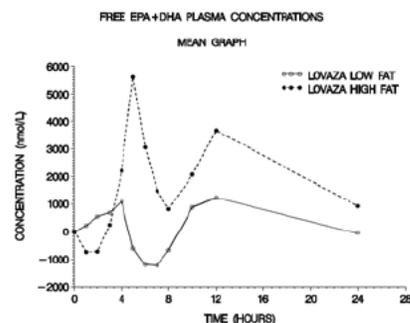
- Less differentiated efficacy of the 3 g/day versus the 2 g/day dose
- Facilitating dose selection across the indications for severe hypertriglyceridemia (TG \geq 500 mg/dL) and persistent hypertriglyceridemia (\geq 200 and $<$ 500 mg/dL while on a statin).
- The 2 and 4 g/day EPANOVA recommendation will make the dosage and administration guidance more straightforward for both physicians and patients, and the available dosages will be consistent across the hypertriglyceridemia indications.

Overview: PK & PD

- **Pharmacokinetics**
 - Linear pharmacokinetics between 2 g and 8 g doses
 - Median T_{max} - EPA: ~ 4.5 – 5.5 h; DHA: 4.7 – 5.3 hrs
 - $T_{1/2}$ – EPA: 4.7 – 10.8 h; DHA: ~7 h
 - Mean EPA and DHA trough levels similar at 16 and 52 weeks of daily dosing of 4 g Epanova
 - approximate 2-fold accumulation of EPA during continued dosing
 - Effect of race on the PK of EPA and DHA not studied
- **Pharmacodynamic Effects**
 - Following oral administration, Epanova (omefas) :
 - decreases the erythrocyte membrane concentration of arachidonic acid (AA) and increases concentrations of EPA and DHA in the erythrocytes
 - decrease serum triglyceride (TG) levels
- **QT**
 - Per agreement from the Agency (letter dated 03Oct2012), in lieu of conducting a thorough QTc study, ECGs were collected during the Phase 3 study (EVOLVE) and evaluated

Major Clin Pharm Studies

- 1. Relative Bioavailability of A Single Dose of Epanova vs. Lovaza After a Low-Fat and High-Fat Meal [Study OM-EPA-001]
 - Design:
 - Single-dose, randomized, open-label, 4-way XO;
7-day washout between treatments
 - Comparisons:
 - 1. Epanova low-fat versus Lovaza low-fat
 - 2. Epanova high-fat versus Lovaza high-fat
 - 3. Epanova high-fat versus Epanova low-fat
 - 4. Lovaza high-fat versus Lovaza low-fat.



OM-EPA-001 Conclusions

- Epanova has a 4-fold greater bioavailability relative to Lovaza[®] during a low-fat diet
- Overall systemic exposure of EPA and DHA appeared to decrease by approximately 15% for Epanova when changing from a high-fat to low-fat diet. For Lovaza, there was a 5-fold difference in AUC for free EPA and DHA between the high-fat vs. low-fat diet

Major Clin Pharm Studies

- 2. MD Epanova on SD Warfarin, and MD Epanova vs. MD Lovaza [Study OM-EPA-006]
 - Design:
 - Cohort 1: Open-label, 2 treatment, 1-sequence; MD Epanova on PK and PD of SD warfarin
 - Cohort 2: Open-label, 1 treatment MD Lovaza;
 - Comparisons:
 - 1. Epanova on the PK and PD of a single 25 mg dose of warfarin
 - 2. Epanova vs. Lovaza (Total EPA, Total DHA, and Total EPA+DHA)

Figure 1 Mean (SD) Plasma R-warfarin Concentrations – Semi-Log Scale

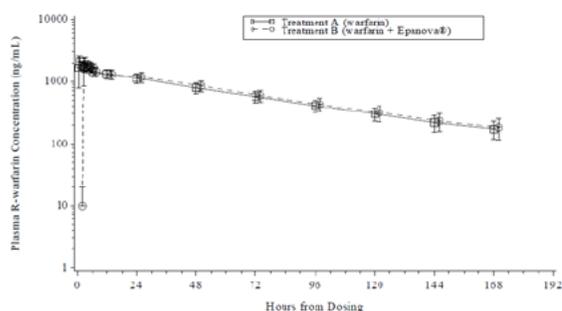


Figure 3 Mean (SD) Plasma S-warfarin Concentrations – Semi-Log Scale

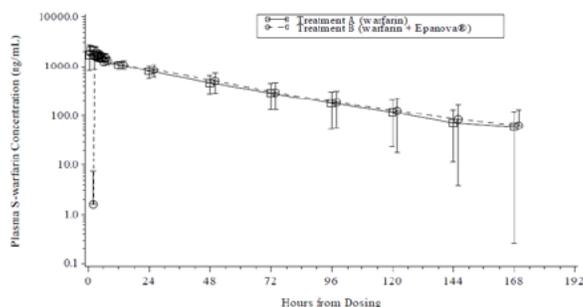


Figure 5 Mean (SD) Warfarin PT INR – Linear Scale

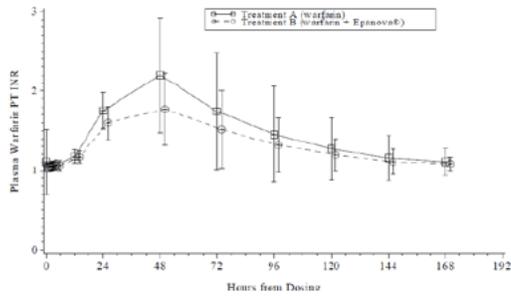


Figure 8 Mean (SD) Baseline-Adjusted Plasma Total EPA Concentrations Semi-Log Scale

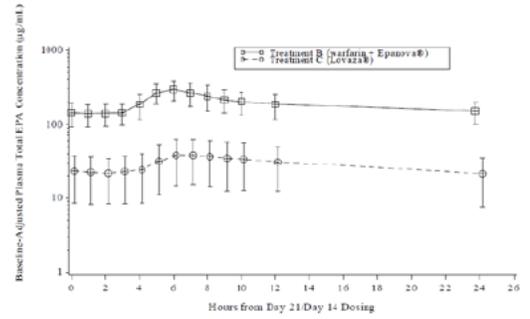


Figure 12 Mean (SD) Baseline-Adjusted Plasma Total DHA Concentrations Semi-Log Scale

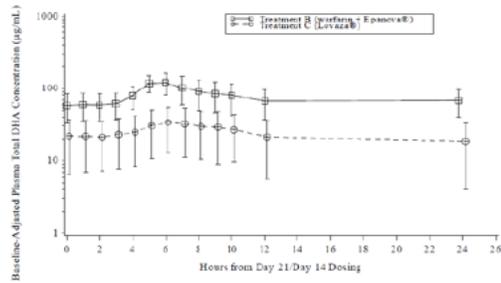
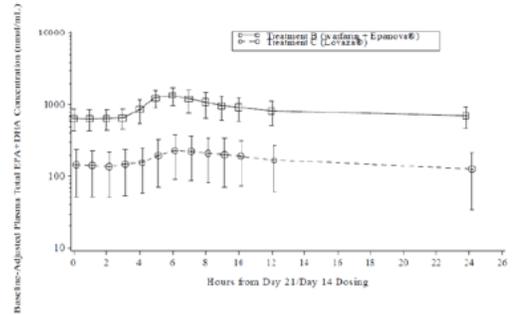


Figure 16 Mean (SD) Baseline-Adjusted Plasma Total EPA+DHA Concentrations Semi-Log Scale



OM-EPA-006 Conclusions

- Once-daily 4 g doses of Epanova[®] for 21 days had no effect on the PK and PD of a single 25 mg dose of warfarin
- Overall exposure (AUC_{0-tau}) to baseline-adjusted Total EPA, Total DHA, and Total EPA+DHA, was approximately 7-, 3-, and 6-fold higher, respectively, with Epanova than with Lovaza

Major Clin Pharm Studies

- 3. MD Epanova on MD Simvastatin [Study OM-EPA-007]
 - Design:
 - Open-label, 2-WXO, MD Epanova and MD Simvastatin in one period and MD simvastatin in another period
 - Comparisons:
 - 1. Epanova on the PK of simvastatin
 - 2. Correlate platelet reactivity and aspirin resistance with circulating levels of fatty acids (EPA, DHA, AA, EPA+DHA and the ratio of EPA to AA [EPA:AA]), and identify potential gene polymorphisms involved in the response)

Figure 1 Mean (SD) Plasma Simvastatin Concentrations – Semi-Log Scale

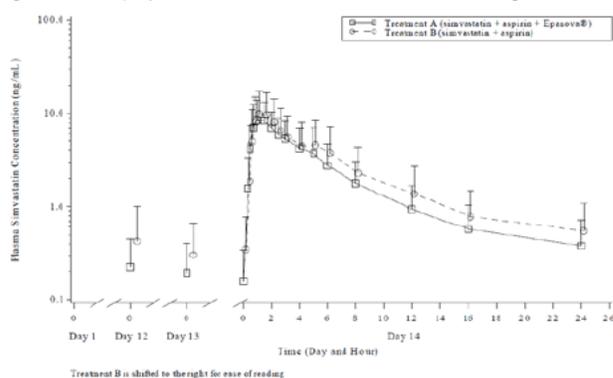
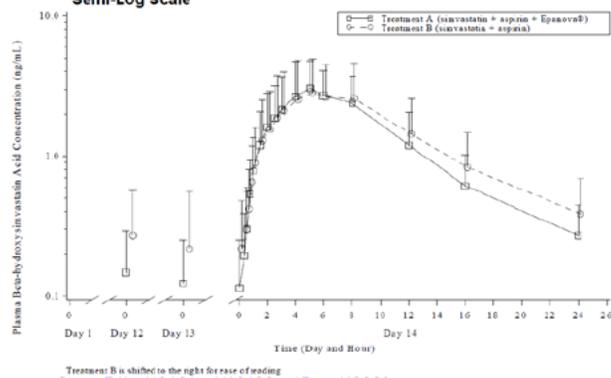


Figure 3 Mean (SD) Plasma Beta-hydroxysimvastatin Acid Concentrations Semi-Log Scale



OM-EPA-007 Conclusions

- Once-daily, 4-g doses of Epanova[®] for 14 days had no effect on the PK of simvastatin and β -OH simvastatin acid following once-daily administration of 40 mg simvastatin and 81 mg aspirin for 14 days
- Concomitant multiple-dose administration of Epanova did not appear to alter the anti-platelet activity of low-dose aspirin.

Overview: Extrinsic/Intrinsic Factors

- **Drug-Drug interaction:** No dose adjustment for warfarin, simvastatin, and aspirin when co-administered with Epanova
 - Concomitant administration of multiple once-daily 4 mg doses of Epanova had no impact on the PK or PD of R- or S-warfarin in plasma following the administration of a single 25 mg dose of warfarin
 - Once-daily, 4-g doses of Epanova for 14 days had no effect on the PK of simvastatin and β -OH simvastatin acid following the once-daily administration of 40 mg of simvastatin and 81 mg of aspirin for 14 days
- **Renal Impairment :** Not studied
- **Hepatic Impairment:** Not Studied
- **Effect of Gender, Age and BW:** (from supportive study SPC-275-4)
 - There was no apparent effect of gender on the pharmacokinetics of EPA or DHA.
 - There appear to be positive relationships between EPA C_{max} (Day 43) and AUC (Days 1 and 43) and age.

Pediatric Plan

- **Sponsor Request**
 - Full waiver of the requirement for studies of pediatric use of Epanova according to 21CFR 315.55(b). The waiver was requested for all pediatric age groups.

Key Questions: Mid Cycle Deliverables

- Is the food-effect (clinical experience, and low-fat/high-fat comparison to lovaza) sufficient?
- What is the exposure-efficacy relationship?
- Were there any bleeding events?
- Is there any need for dose adjustment based on intrinsic factors?
- Is there any need for dose adjustment based on extrinsic factors?



Information Requested

- Bioanalytical report for Study SPC-275-4

Conclusions

- This NDA is filable from OCP perspective
- No OSI inspection is requested



Backup Slides



Study OM-EPA-001

Table 11.4-4 Summary ANOVA Results (Total EPA+DHA)

Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)											
Ln-Transformed data											
Total EPA+DHA (nmol/mL)											
A vs. B analyses		Baseline-Adjusted Results					Unadjusted Results				
		LSM A	LSM B	A/B [†]	90% CI		LSM A	LSM B	A/B [†]	90% CI	
					Lower	Upper				Lower	Upper
Low-Fat Epanova [®] vs. Lovaza [®]	AUC _{0-t}	2850.16	661.95	400.36 p<0.0001	326.87	490.36	8161.12	6288.70	129.77 p<0.0001	124.49	135.28
	AUC _{0-inf}	5219.56	803.42	649.66	511.75	824.75	-	-	-	-	-
	C _{max}	225.79	61.08	389.66	301.74	452.86	466.36	305.82	152.50	140.47	165.55
High-Fat Epanova [®] vs. Lovaza [®]	AUC _{0-t}	4604.02	3589.47	128.26 p<0.0001	116.85	140.80	10405.85	9410.46	110.58 0.0001	106.45	114.87
	AUC _{0-inf}	8575.57	7924.29	108.22	81.34	143.98	-	-	-	-	-
	C _{max}	543.22	401.94	135.15	118.39	154.29	800.75	654.94	122.26	111.74	133.77
Epanova [®] low-fat vs. high-fat	AUC _{0-t}	2571.45	4599.14	55.90 p<0.0001	48.70	64.20	8001.25	10406.52	76.90 p<0.0001	73.15	80.81
	AUC _{0-inf}	4971.04	8714.53	57.00	42.27	76.97	-	-	-	-	-
	C _{max}	213.68	543.13	39.30	32.49	47.64	453.39	801.04	56.60	51.04	62.77
Lovaza [®] low-fat vs. high-fat	AUC _{0-t}	655.97	3468.04	18.90 p<0.0001	15.81	22.62	6293.48	9473.14	66.40 p<0.0001	62.66	70.44
	AUC _{0-inf}	369.03	13226.05	2.80	0.11	73.60	-	-	-	-	-
	C _{max}	61.00	399.12	15.30	12.38	18.87	306.56	656.53	46.70	42.10	51.79

[†]Treatment ANOVA p-value presented for AUC_{0-t}.

Table 11.4-5 Summary ANOVA Results (Free EPA)

Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)											
Ln-Transformed data											
Free EPA (ng/mL)											
A vs. B analyses		Baseline-Adjusted Results					Unadjusted Results				
		LSM A	LSM B	A/B [†]	Lower 90% CI		LSM A	LSM B	A/B [†]	Lower 90% CI	
					Upper	Upper				Upper	Upper
Low-Fat Epanova [®] vs. Lovaza [®]	AUC _{0-t}	4878.77	617.63	789.92 p<0.0001	598.68	1042.25	7098.72	2620.01	270.94 p<0.0001	237.49	309.11
	AUC _{0-inf}	-	-	-	-	-	-	-	-	-	-
	C _{max}	588.25	77.45	759.54	594.00	971.22	897.21	171.10	407.48	335.66	494.66
High-Fat Epanova [®] vs. Lovaza [®]	AUC _{0-t}	8250.11	4250.50	194.19 p<0.0001	172.96	217.82	10153.46	6281.56	161.64 p<0.0001	149.34	174.96
	AUC _{0-inf}	9824.45	6166.79	159.31	118.92	213.43	-	-	-	-	-
	C _{max}	1225.63	569.66	215.15	185.45	249.61	1310.69	661.23	198.22	173.45	226.53
Epanova [®] low-fat vs. high-fat	AUC _{0-t}	4671.67	8250.11	56.60 p<0.0001	47.03	68.18	6972.95	10153.46	68.68 p<0.0001	60.02	78.58
	AUC _{0-inf}	5669.14	9072.85	62.50	48.81	79.99	-	-	-	-	-
	C _{max}	572.59	1225.63	46.70	36.90	50.00	680.68	1310.69	51.93	42.17	63.95
Lovaza [®] low-fat vs. high-fat	AUC _{0-t}	617.51	4541.09	13.60 p<0.0001	10.67	17.34	2625.59	6361.83	41.27 p<0.0001	37.23	45.75
	AUC _{0-inf}	4269.37	4586.43	85.60	1.37	5344.91	-	-	-	-	-
	C _{max}	71.79	570.45	13.60	11.05	16.83	171.77	663.89	25.87	22.08	30.32

[†]Treatment ANOVA p-value presented for AUC_{0-t}.

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Figure 6: Relationship between mean EPA Cmax and AUC₀₋₄ and dose of Epanova SGC after administration of the initial dose (Day 1) during oral administration of Epanova SGC to healthy volunteers for 43 days.

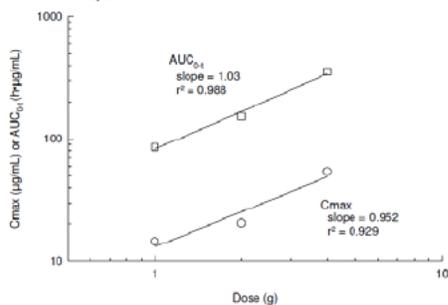


Figure 7: Relationship between mean EPA Cmax and AUC₀₋₁₂ and dose of Epanova SGC after administration of the final dose (Day 43) during oral administration of Epanova SGC to healthy volunteers for 43 days.

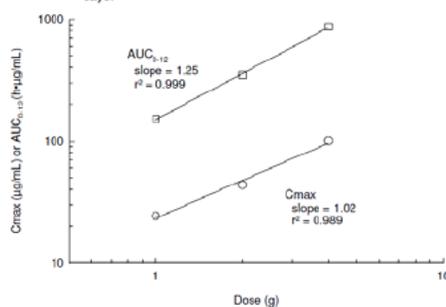


Figure 10: Relationship between mean DHA Cmax and AUC₀₋₄ and dose of Epanova SGC after administration of the initial dose (Day 1) during oral administration of Epanova SGC to healthy volunteers for 43 days.

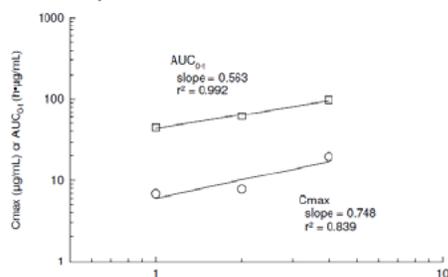
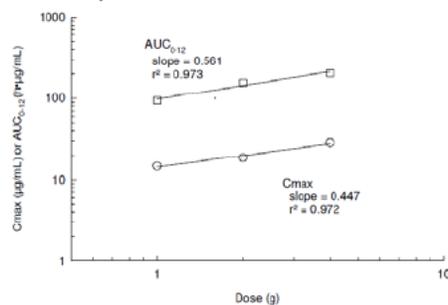


Figure 11: Relationship between mean DHA Cmax and AUC₀₋₁₂ and dose of Epanova SGC after administration of the final dose (Day 43) during oral administration of Epanova SGC to healthy volunteers for 43 days.



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Figure 12: Change from baseline in erythrocyte membrane concentration of arachidonic acid during administration of placebo, Epanova SGC, Epanova (b) (4) and Maxepa to healthy volunteers for 43 days.

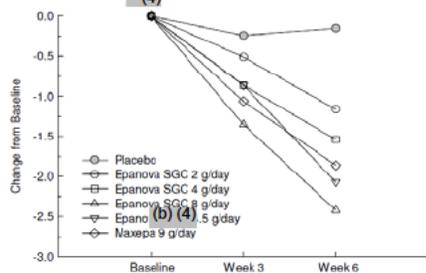


Figure 13: Change from baseline in erythrocyte membrane concentration of EPA during administration of placebo, Epanova SGC, Epanova (b) (4) and Maxepa to healthy volunteers for 43 days.

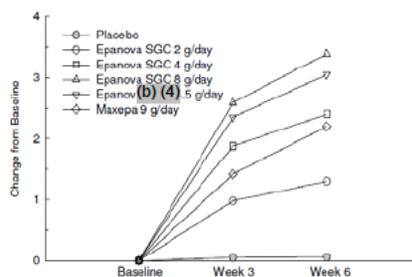
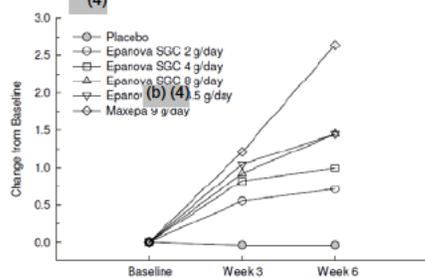


Figure 14: Change from baseline in erythrocyte membrane concentration of DHA during administration of placebo, Epanova SGC, Epanova (b) (4) and Maxepa to healthy volunteers for 43 days.



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Figure 1: Individual subject dose-normalized EPA Cmax on Day 1 after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.

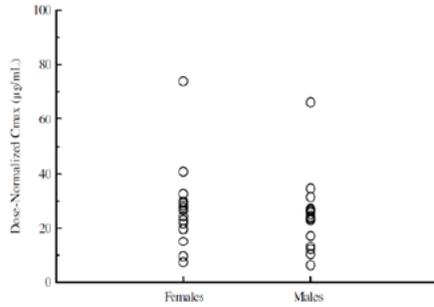


Figure 2: Individual subject dose-normalized EPA AUC on Day 1 after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.

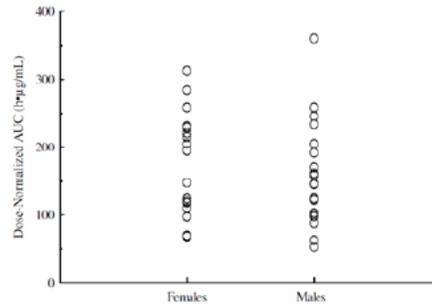


Figure 3: Individual subject dose-normalized EPA Cmax on Day 43 after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.

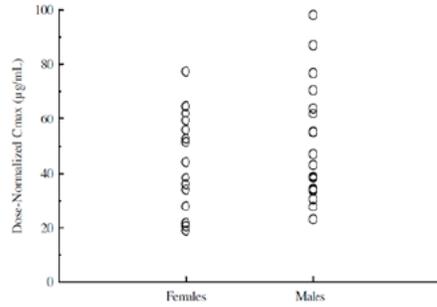
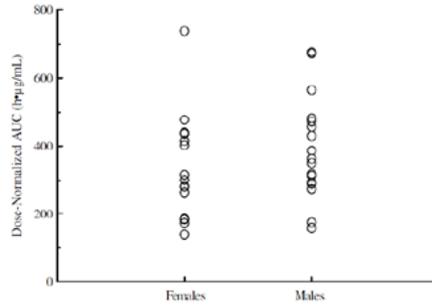


Figure 4: Individual subject dose-normalized EPA AUC on Day 43 after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.



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Figure 10: Relationship between dose-normalized EPA Cmax on Day 43 and age after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.

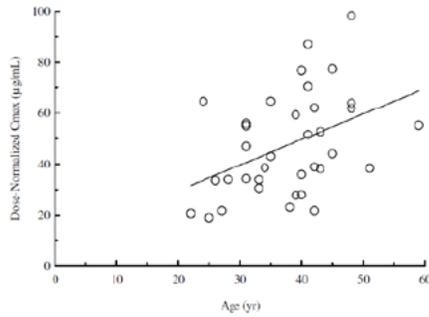


Figure 9: Relationship between dose-normalized EPA AUC on Day 1 and age after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.

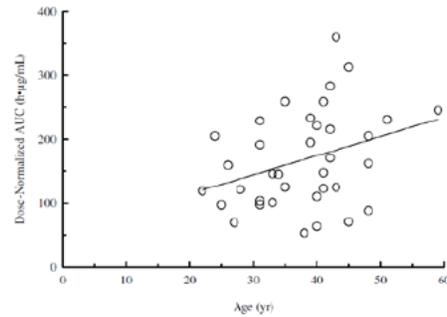


Figure 12: Relationship between dose-normalized DHA Cmax on Day 43 and body weight after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.

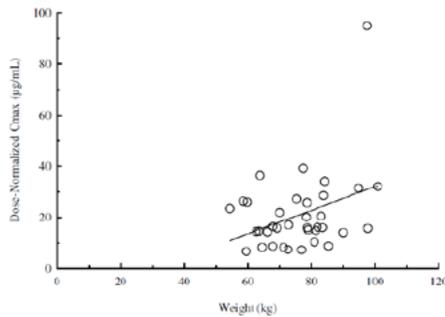
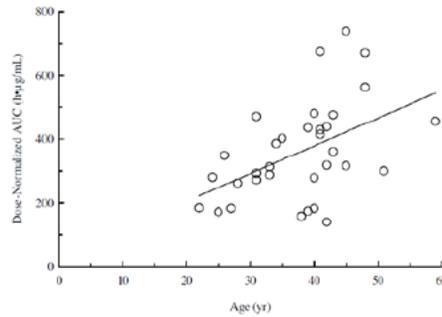


Figure 11: Relationship between dose-normalized EPA AUC on Day 43 and age after oral administration of Epanova Soft Gelatin Capsules to healthy male and female volunteers.



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/s/

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09/04/2013

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