CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202057Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	202057
Submission Date:	September 26, 2011
Brand Name:	Vascepa™
Generic Name:	Icosapent ethyl (ethyl-EPA)
Formulation/Strength:	Capsule/1 g
OCP Reviewer:	Zhihong Li, Ph.D.
OCP Team Leader:	Immo Zadezensky, Ph.D. (acting)
OCP Division:	Division of Clinical Pharmacology 2
OND Division:	Division of Metabolism and Endocrinology Products
Sponsor:	Amarin Pharmaceuticals Ireland Limited
Submission Type; Code:	505(b)(2), standard review
Dosing regimen:	2 g BID
Indication:	As an adjunct to diet to reduce triglyceride (TG) levels in patients with very high (≥500 mg/dL) triglycerides

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Abbreviation	Term
AA	arachidonic acid, C20:4(n-6)
ALA	α-linolenic acid, C18:3(n-3)
AMR101	Vascepa, Miraxion, LAX-101
ApoB	apolipoprotein B
AUC	area under the curve
AUC_{INR}	area under the INR versus time curve
BMI	body mass index
CE	cholesteryl ester
CI	confidence interval
CL/F	apparent total plasma clearance after oral administration (F is the oral bioavailability)
CoA	coenzyme A
COX	cyclooxygenase
C_{max}	maximum concentration
C_{min}	trough (predose) concentration
CYP	cytochrome P450
CVD	cardiovascular disease
DAG	diacylglycerol
DDI	drug-drug interaction
DHA	docosahexaenoic acid, C22:6(n-3)
DPA	ω-3 docosapentaenoic acid, C22:5(n-3)
Ethyl-EPA	ethyl eicosapentaenoate, EPA-E
EPA	eicosapentaenoic acid, C20:5(n-3)
FABP	fatty-acid binding proteins
FFA	free fatty acid
GC/FID	gas chromatography with flame ionization detection
INR	International Normalized Ratio
INR_{max}	maximum INR value
LAX-101	AMR101, Vascepa, Miraxion
LDL	low-density lipoprotein
PL	phospholipids
RBC	red blood cell
TAG	triacylglycerol
TG	triglyceride
VLDL	very low-density lipoprotein

1 EXECUTIVE SUMMARY

Amarin Pharmaceuticals Ireland Limited (hereafter Amarin/the sponsor) submitted a New Drug Application (NDA) 202057 for Vascepa™ (icosapent ethyl, ethyl-EPA) capsules for the treatment of patients with very high triglycerides (≥500 mg/dL). The proposed indication is "as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) triglycerides". Vascepa is available at one dose strength, 1 g as amber-colored soft-gelatin capsules. The daily dose of Vascepa is 4g/day taken as two 1 gram capsules twice daily (BID).

This application is submitted by the sponsor as a 505(b)(2) NDA. This NDA does not rely on data from any product already approved or marketed in the US, nor does the application rely on the FDA's findings of safety and effectiveness for any product approved in the US. The nonclinical section contains toxicology publications to which Amarin does not have right of reference. Amarin therefore relies on this literature to support the safety of the product and to be used in support of product labeling.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the NDA 202057 for Vascepa™ submitted on September 26, 2011. The clinical pharmacology information submitted under this NDA is acceptable.

1.2 PHASE IV COMMITMENTS

None.

1.3 CLINICAL PHARMACOLOGY SUMMARY

A total of 7 clinical pharmacology studies or studies with clinical pharmacology components were conducted in support of the hypertriglyceridemia indication, two single/multiple dose PK studies, three DDI studies, and two Phase 3 studies in patients with hypertriglyceridemia.

After oral administration, ethyl-EPA is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of total EPA were reached approximately 5 hours following oral doses of ethyl-EPA. The mean terminal half-life of total EPA in plasma was long, approximately 89 hours based on baseline-adjusted concentrations. Steady state was approximately reached by Day 14.

Three phase 1, open-label, crossover, drug-drug interaction studies were conducted with or without steady-state ethyl-EPA at 4 g/day (2g BID); one study between ethyl-EPA and omeprazole (CYP2C19 substrate) or rosiglitazone (CYP2C8 substrate) where subjects were administered omeprazole 40 mg/day QD for 7 days or a single 8 mg dose of rosiglitazone; one study between ethyl-EPA and warfarin where a single dose of 25 mg racemic warfarin (S-warfarin is a probe substrate for CYP2C9) was administered; and one study between ethyl-EPA and atorvastatin (CYP3A4 substrate) where subjects received atorvastatin 80 mg QD for 7 days.

The ratios of the geometric means of C_{max} and AUC are listed in the following Table 1. No significant increase in omeprazole, rosiglitazone, S-warfarin, or atorvastatin exposure was observed, it is concluded that 4 g/day ethyl-EPA does not inhibit the metabolism of omeprazole, rosiglitazone, S-warfarin, or atorvastatin.

The anticoagulation pharmacodynamic parameters of warfarin and their comparisons with and without ethyl-EPA were also evaluated. The ratio of the geometric means of INR_{max} following administration of warfarin with and without ethyl-EPA was 0.87, while the same ratio for AUC_{INR} was 0.94. The 90% confidence intervals were all between 80% and 125%. It is concluded that 4 g/day ethyl-EPA does not significantly affect the anticoagulation parameters of warfarin.

Table 1 Ratios of the Geometric Means of C_{max} and AUC of Selected CYP Substrates in the Presence and Absence of ethyl-EPA (4 g/day)

Substrate	C_{max} Ratio (90% CI)	AUC* Ratio (90% CI)
omeprazole	1.01 (87.4, 116.3)	0.84 (76.0, 91.9)
rosiglitazone	1.01 (92.0, 109.9)	0.90 (87.0, 93.4)
R-warfarin	1.08 (99.1, 117.4)	0.99 (95.7, 102.9)
S-warfarin	1.11 (101.3, 120.6)	1.00 (96.5, 103.2)
atorvastatin	1.08 (94.9, 122.1)	0.99 (90.2, 108.9)
2-hydroxy atorvastatin	1.04 (89.1, 121.3)	0.91 (82.8, 99.7)
4-hydroxy atorvastatin	0.97 (78.0, 117.3)	0.92 (82.3, 102.8)

Ratios are geometric mean ratios of treatment with Vascepa / treatment without Vascepa.
* AUC refers to AUC_{τ} for omeprazole, atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin where $\tau = 24$ hr; and refers to $AUC_{0-\infty}$ for rosiglitazone, R-warfarin and S-warfarin
CI = confidence interval in percent

EPA trough concentrations at week 12 were analyzed in the two phase 3 studies MARINE and ANCHOR. Gender effect on EPA exposure was evaluated and it was found that plasma total EPA concentrations did not differ significantly between men and women.

Patients younger and older than 65 years were included in ethyl-EPA phase 3 clinical trials. In the MARINE study, subgroup analyses by age were not meaningful due to the small number of patients over the age of 65 years (18 patients were >65 years of age). In the ANCHOR study, 32 geriatric patients showed higher exposure than 39 patients who were younger than 65 years old at the 4 g/day dose. However, at the 2 g/day dose, plasma total EPA exposure was not significantly different between these two age groups (33 patients ≥65 and 40 patients <65 years). The clinical significance of this is unknown.

2 QUESTION BASED REVIEW

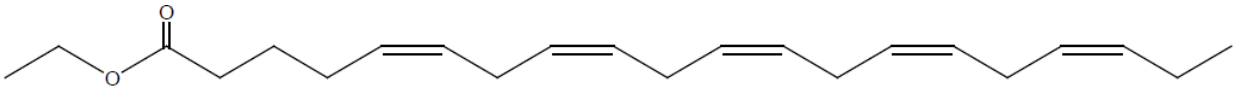
2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug substance: icosapent ethyl (ethyl-EPA hereafter)

The chemical name for icosapent ethyl is ethyl (5Z,8Z,11Z,14Z,17Z)-5,8,11,14,17-icosapentaenoate. Icosapent ethyl is a clear, colorless to pale yellow liquid. Icosapent ethyl is insoluble in water and highly soluble in various organic solvents.

1. Structural formula:



2. Molecular formula: $C_{22}H_{34}O_2$
3. Molecular weight: 330.51

Drug product: AMR101 capsules

The drug product, AMR101 capsules, 1 g, is an oblong shaped, (b) (4) soft gelatin capsule for oral administration.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Ethyl-EPA is converted to free EPA by esterases, and then incorporated into phospholipids, cholesteryl esters and triglycerides in the blood and other tissues. A single mechanism of action to explain the hypotriglyceridemic effects of omega-3 fatty acid has not been identified. Instead, multiple pharmacologic effects are involved. Results from preclinical and clinical studies suggest that EPA 1) reduces hepatic very low-density lipoprotein triglyceride (VLDL-TG) synthesis or secretion and 2) enhances TG clearance from circulating VLDL particles. Studies have shown that EPA reduces TG synthesis or secretion by decreasing lipogenesis, increasing β-oxidation of fatty acids, and increasing degradation of apoB-100. EPA also accelerates TG clearance by increasing lipoprotein lipase (LPL) activity, which promotes removal of TG from VLDL.

2.1.3 What are the proposed dosage and route of administration?

The daily dose of Vascepa is 4g/day taken as two 1 gram capsules twice daily (BID). (b) (4)

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A total of 7 clinical/clinical pharmacology studies were conducted in support of the hypertriglyceridemia indication, five studies in healthy volunteers and two Phase 3 studies in patients with hypertriglyceridemia. The key design features of these studies were summarized in Table 2 and Table 3.

Healthy Volunteer Studies:

- One single and multiple dose PK study (Study LA01.01.0009) and one multiple dose PK study (Study AMR-01-01-0018): Study LA01.01.0009 was conducted at 2 g/day ethyl-EPA in support of the CNS program but is also relevant for the hypertriglyceridemia program; Study AMR-01-01-0018 was conducted with 2 and 4 g/day ethyl-EPA, specifically in support of the hypertriglyceridemia program.

- Three DDI studies to investigate the effect of ethyl-EPA on the PK of substrates for the following CYPs:

  ○ The CYP2C19 substrate omeprazole and the CYP2C8 substrate rosiglitazone (both in Study AMR-01-01-0020)

  ○ The CYP2C9 substrate warfarin (Study AMR-01-01-0021). The effect of ethyl-EPA on the anti-coagulation pharmacodynamics of warfarin was also investigated in this study.

  ○ The CYP3A4 substrate atorvastatin, a common concomitant medication with ethyl-EPA (Study AMR-01-01-0023)

Phase 3 Studies in Patients with Elevated Triglyceride Levels:

- One study in patients with very high levels of TG (≥500 mg/dL and ≤2000 mg/dL) (MARINE study)
- One study in patients with high levels of TG (≥200 mg/dL to 499 mg/dL) (ANCHOR study)

Table 2 PK Studies in Healthy Volunteers

Study ID	Study Objective	Study Design	Subjects No. (M/F) Age (range or mean in years)	Dose, Dosage Form, Route of Administration [Product Batch ID*]	Sample Type	Analyte	Assay
LA01.01.0009	Safety & PK	Phase 1, single-center, open-label, randomized, single and repeated dose study	Group A 12 M Mean 33 yr	SD of 2 g (four 0.5 g Vascepa capsules) on Day 1 + MD of 2 g/day (four 0.5 g Vascepa capsules QD) on Days 3-30 [212797AR1]	Plasma RBC	Total EPA	GC/FID (in µg/g)
			Group B 12 M Mean 33 yr	SD of 2 g (four 0.5 g Vascepa capsules) on Days 1 and 30 + MD of 2 g/day (four 0.5 g Vascepa capsules QD) on Days 3-29 [212797AR1]	Plasma RBC	Total EPA	
AMR-01-01-0018	PK	Phase 1, single-center, open-label, randomized, repeated dose study	48 Subjects 24 M/24 F, 20 to 55 yr	2 g/day: one 1 g Vascepa capsule BID [256189A]	Plasma Plasma RBC	Total EPA Unesterified EPA Total EPA	LC/MS-MS (in µg/mL)
				4 g/day: two 1 g Vascepa capsules BID [256189A]			
				2 g/day: two 1 g Vascepa capsules QD [256189A]			
				2 g/day: two 0.5 g Vascepa capsules BID [231171A]			
AMR-01-01-0020	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	30 Subjects 19 M/11F 20 to 55 yr	Omeprazole With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Omeprazole	LC/MS-MS
				Rosiglitazone With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Rosiglitazone	LC/MS-MS
AMR-01-01-0021	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	26 Subjects 20 M/6 F 20-55 yr	Warfarin With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	R-warfarin S-warfarin	LC/MS-MS
AMR-01-01-0023	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	30 Subjects 22 M/8 F 20-54 yr	Atorvastatin With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Atorvastatin, 4-hydroxy-atorvastatin, 2 hydroxy-atorvastatin -	LC/MS-MS

HV = healthy volunteers; P = patients; M/F = males/females; EPA = eicosapentaenoic acid; RBC = red blood cells; SD = single dose; MD = multiple dose
* Bulk capsule lot number;
† Plasma samples at a few time points were also analyzed for total and unesterified EPA by LC/MS-MS.

Table 3 Studies in Hypertriglyceridemic Patients with PK Measurements

Study ID	Study Objective	Study Design	Subjects No. (M/F) Age (range years)	Dose, Dosage Form, Route of Administration [Product Batch ID*]	Sample Type	Analyte	Assay
AMR-01-01-0016 (MARINE)	Safety/Efficacy & PK	Phase 3, multi-center, double-blind, placebo-controlled, randomized, repeated-dose	229 Patients (175 M/54 F) 27 to 79 yr	Placebo [XI07A1 and XI07A2]	Plasma RBC	Total EPA	LC/MS-MS (in µg/mL)
				2 g/day: one 1 g Vascepa oral capsule BID [XI07A1, XI07A2, XI07B2, XI07B3]			
				4 g/day: two 1 g Vascepa capsules BID [XI07B2 and XI07B3]			
AMR-01-01-0017 (ANCHOR)	Safety/Efficacy & PK	Phase 3, multi-center, double-blind, placebo-controlled, randomized, repeated-dose	702 Patients (431 M/271 F) 31 to 88 yr	Placebo [XI07A1 and XI07A2]	Plasma RBC	Total EPA	LC/MS-MS (in µg/mL)
				2 g/day: one 1 g Vascepa oral capsule BID [XI07A1, XI07A2, XI07B2, XI07B3]			
				4 g/day: two 1 g Vascepa capsules BID [XI07B2 and XI07B3]			

HV = healthy volunteers; M/F = males/females; EPA = eicosapentaenoic acid; RBC = red blood cells
* Bulk capsule lot number

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

Not applicable.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Total plasma EPA, unesterified plasma EPA, and RBC EPA levels were appropriately measured using validated analytical methods for pharmacokinetic parameters. See section 2.4 Analytical Section for details.

However, there are limitations in the interpretation of pharmacokinetic parameters because of the variances of baseline EPA levels, use caution in interpreting EPA PK parameters.

Poly-unsaturated fatty acids of both the omega-3 and omega-6 classes are essential dietary components but cannot be synthesized *de novo* in the body. Since EPA is a component of the normal diet, it is absorbed from the diet and is naturally present in plasma and red blood cells (RBCs) (baseline EPA concentrations). Baseline concentrations of EPA in plasma and tissues are a reflection of food intake. Marine fish is the single most important source of dietary omega-3 fatty acid intake (including EPA). Therefore, endogenous EPA concentrations are higher in subjects with high consumption of marine fish.

It has been reported that endogenous plasma levels of EPA in western subjects are approximately 30 μg/mL for total EPA and 0.4 μg/mL for unesterified EPA, although up to a 100-fold difference in concentration was noted between subjects [1]. In populations known to consume large quantities of fish, the EPA plasma concentrations are usually much higher. For example, in a Japanese clinical study, the group-mean endogenous total EPA plasma concentrations were 93 and 97 μg/mL [2].

Measures have been used in sponsor submitted studies to maintain stable EPA baseline levels. In study AMR-01-01-0018, subjects were asked to maintain their current dietary regime, and to not alter their normal activity routines through the duration of the study, and to consume no more than two servings of oily fish per week. In the MARINE (Study AMR-01-01-0016) and ANCHOR (Study AMR-01-01-0017) studies, the screening period included a 4- to 6-week diet and lifestyle stabilization and washout period. Patients were also asked to maintain stable diet and physical activity level throughout the study.

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[1] Bowen CL, Kehler J, Evans CA. Development and validation of a sensitive and selective UHPLC-MS/MS method for simultaneous determination of both free and total eicosapentaeonic acid and docosahexenoic acid in human plasma. Journal of chromatography B, Analytical technologies in the biomedical and life sciences. 2010;878(30):3125-33. Epub 2010/10/29.

[2] Itakura H, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, et al. Relationships between plasma fatty acid composition and coronary artery disease. J Atheroscler Thromb. 2011;18(2):99-107. Epub 2010/11/26.

In study AMR-01-01-0018 (healthy volunteers), high variances in EPA concentrations were found. The mean ±SD baseline total EPA plasma concentration (study-wide mean, N=44) was 15 ±15 µg/mL, and the study-wide mean ±SD baseline unesterified EPA plasma concentration was 0.10 ±0.10 µg/mL. In the MARINE study and ANCHOR study, high variances in EPA concentrations were also found at baseline and week 12 (Table 4 and Table 5).

Table 4 MARINE Study: Trough EPA Plasma and RBC Concentrations (µg/mL) at Baseline and Week 12

Treatment	Matrix[1]	N[2]	Baseline Mean[3] (SD)	Week 12 Endpoint Mean[4] (SD)
Placebo	Plasma	61	57.7 (42.73)	52.8 (40.03)
	RBC	64	14.7 (9.27)	11.6 (8.69)
2 g/day Vascepa	Plasma	62	63.6 (51.36)	185.0 (96.88)
	RBC	61	15.7 (9.92)	44.9 (20.47)
4 g/day Vascepa	Plasma	69	61.2 (67.44)	326.7 (205.70)
	RBC	66	16.0 (9.16)	71.6 (31.54)

Table 5 ANCHOR Study: Trough EPA Plasma and RBC Concentrations (µg/mL) at Baseline and Week 12

Treatment	Matrix[1]	N[2]	Baseline Mean[3] (SD)	Week 12 Endpoint Mean[4] (SD)
Placebo	Plasma	81	28.1 (28.01)	30.6 (27.90)
	RBC	79	11.2 (6.64)	9.9 (5.70)
2 g/day Vascepa	Plasma	73	28.1 (13.71)	123.8 (67.82)
	RBC	71	10.9 (5.21)	43.7 (16.84)
4 g/day Vascepa	Plasma	71	28.1 (18.79)	182.6 (71.73)
	RBC	69	11.6 (5.56)	72.7 (31.49)

2.2.4 Exposure-response

No Exposure-response relationship was assessed in this program.

2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

After ingestion of ethyl-EPA, the compound is totally hydrolyzed and converted into EPA by pancreatic lipase in the small intestine. Total and/or unesterified EPA levels were measured in the plasma and RBC. No EPA metabolite level was measured.

2.2.5.1 What are the single dose and multiple dose PK parameters?

PK characteristics are summarized in the following ADME sections.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

No direct comparison was made between healthy volunteers and patients.

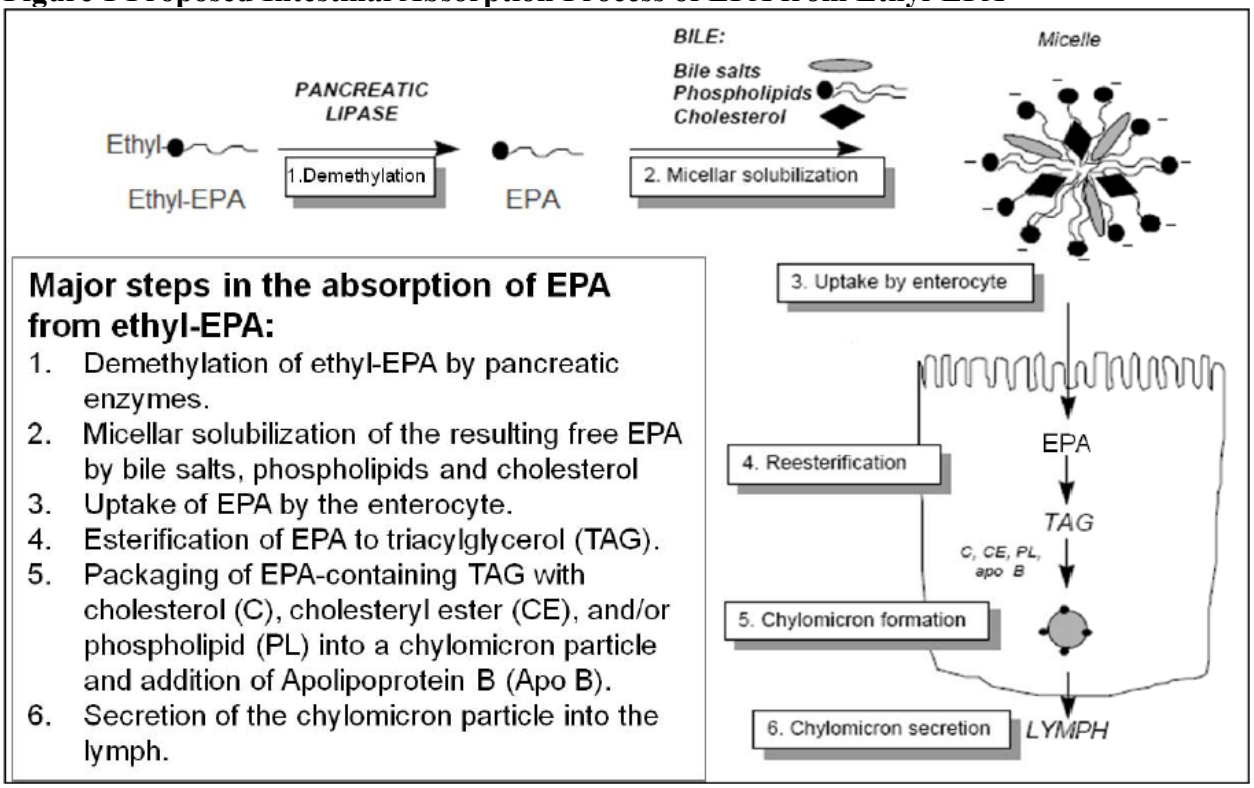
2.2.5.3 What are the characteristics of drug absorption?

After ingestion of ethyl-EPA, the compound is totally hydrolyzed and converted into EPA by pancreatic lipase in the small intestine. Free long-chain fatty acids including EPA together with other components such as monoglycerides, dietary cholesterol and phospholipids (PL), and bile

salts form mixed micelles. Mixed micelles in close proximity to enterocytes deliver their contents including free fatty acids such as EPA for absorption. Long-chain fatty acids released from micelles bind to water-soluble fatty acid-binding proteins (FABP) of their plasma membrane, which helps to transfer them across the membrane into the cytoplasm.

Once inside the enterocytes, EPA enters the endoplasmic reticulum, where EPA-containing triglycerides (TG) are formed which along with cholesterol and PL are incorporated into chylomicrons. Since chylomicrons are water soluble, they are able to leave the mucosal cells via exocytosis and enter the lymphatic system in the submucosa, where they are transported to the thoracic duct and enter the systemic circulation. A small percentage of fatty acids are absorbed directly into the blood through the liver.

Figure 1 Proposed Intestinal Absorption Process of EPA from Ethyl-EPA



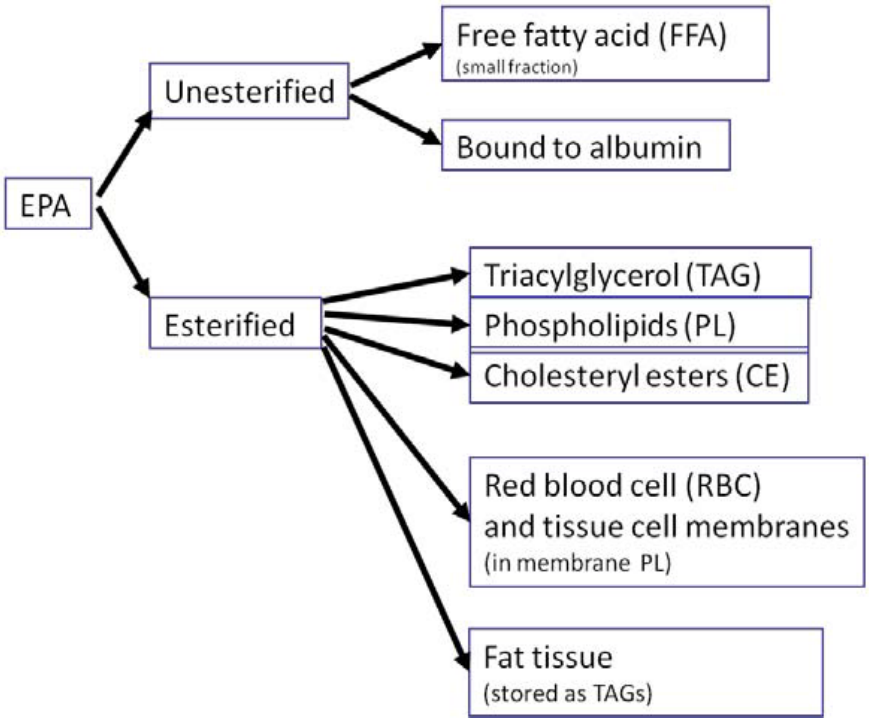
The sponsor conducted *in vitro* transport studies; EPA does not appear to be either a substrate for or an inhibitor of major transporters including P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, and OATP1B3 (Study OPT-2010-157). No transporter mediated drug-drug interactions are expected and clinical studies investigating transporter-mediated interactions were not conducted.

2.2.5.4 What are the characteristics of drug distribution?

After absorption, EPA is distributed and incorporated into circulating PL, TAG and CE, and in the phospholipid components of cell membranes. In red blood cells (RBCs), almost all EPA is incorporated into PL of the cell membrane. Only a small fraction of the total circulating EPA concentration is unesterified, i.e., not incorporated in TAG, PL, CE, and RBCs. Figure 2 shows

the different chemical forms of EPA in the body. EPA like other fatty acids also exists in very-low-density lipoproteins (VLDL) and low-density lipoproteins (LDL) after processing in the liver, mostly under the form of TAG.

Figure 2 Chemical Forms of EPA in the Body



The *in vitro* binding of EPA to human plasma proteins and the partitioning of EPA into RBCs were investigated (Study 789867). The mean *in vitro* plasma protein binding of EPA at clinically relevant concentrations of 0.75 to 15.0 µg/mL ranged from 98.8% to 99.8% in human plasma. Partitioning into RBCs was low and independent of concentration. The plasma to blood ratio was greater than 1, indicating that EPA was predominantly distributed in the plasma fraction.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted.

2.2.5.6 What are the characteristics of drug metabolism?

A simplified scheme of the major pathways of metabolism and bio-activation of EPA from ethyl-EPA is shown in Figure 3. EPA is metabolized by a number of biochemical pathways that include:

• β-oxidation: EPA is primarily metabolized by β-oxidation. β-oxidation is the fatty acid catabolism process in which two carbon fragments are removed from the fatty acid chain in each cycle, producing acetyl CoA which can then travel through the Krebs cycle (citric acid cycle) or be synthesized into ketones and used as energy. Intermediate products of this process are chain-shortened fatty acid metabolites but the end products are carbon dioxide (CO_2) and water,

principally excreted in expired breath. Fatty acids are oxidized by most the tissues in the body, with some exceptions such as the brain (which can hardly utilize fatty acids for energy requirements) and erythrocytes.

• Chain elongation to docosapentaenoic acid (DPA), and further desaturation to docosahexaenoic acid (DHA) (see Figure 4): EPA is converted into DPA and DHA, although DHA also undergoes reverse metabolism (retroconversion) back to EPA. These reactions occur primarily in the endoplasmic reticulum of the liver.

• Cytochrome P450 (CYP)-mediated hydroxylations and oxidations to hydroxy- and epoxy-metabolites, with subsequent hydrolysis to vicinal diols (Figure 5). The CYP-dependent enzymes shown to metabolize EPA as an alternative substrate to AA include:

• AA hydroxylases:

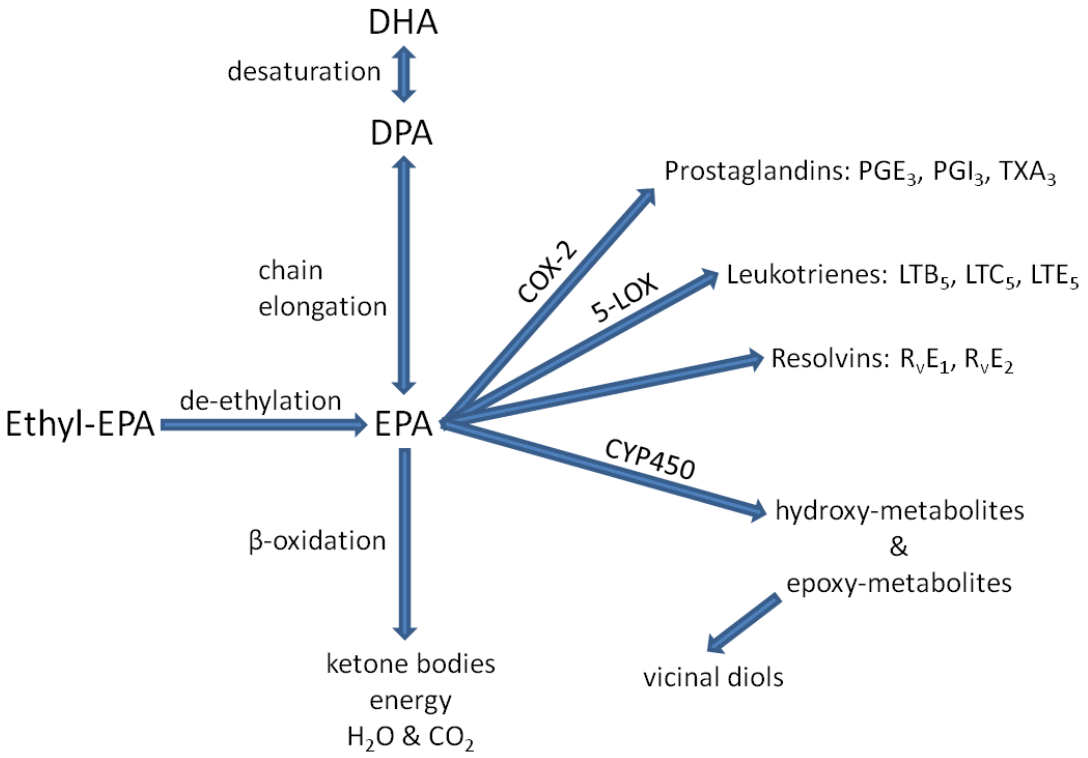
  ▪ ω-hydroxylases include the human isoforms of the CYP4A/4F family: 4A11, 4F2, and 4F3A, found mainly in the liver and kidney.
  ▪ (ω-1)-hydroxylases include human CYPs 1A1, 1A2, 2E1, 4F8, and 4F12.

• AA epoxygenases include the human isoforms of the CYP2C/2J family: 2C8, 2C9, 2C18, 2C19, and 2J2.

• Biosynthesis of EPA-derived eicosanoids, which are among the mediators and regulators of inflammation. EPA can also act as a substrate for both COX and LOX, giving rise to eicosanoids with a slightly different structure from those formed from AA, resulting in an increased production of EPA-derived eicosanoids from the 3-series prostaglandins/thromboxanes (PGE3, PGI3, TXA3), 5-series leukotrienes (LTB5, LTC5, LTE5), and E-series resolvins (RvE1, RvE2) (Figure 3).

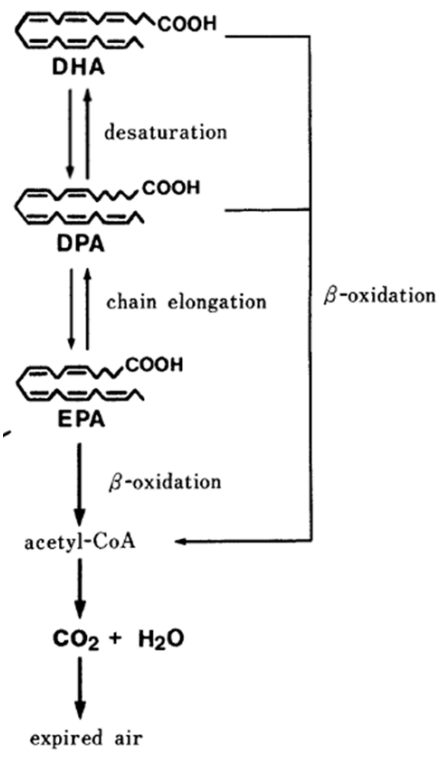
Although the CYP-mediated and COX/LOX-mediated pathways acting on EPA may constitute bio-activation leading to metabolites of EPA with unique activities, their contributions to the metabolism of EPA in the overall elimination of EPA are quantitatively less important. The major pathway of elimination of EPA is β-oxidation.

Figure 3 Pathways of Hydrolysis of Ethyl-EPA and Metabolism/Bio-activation of EPA



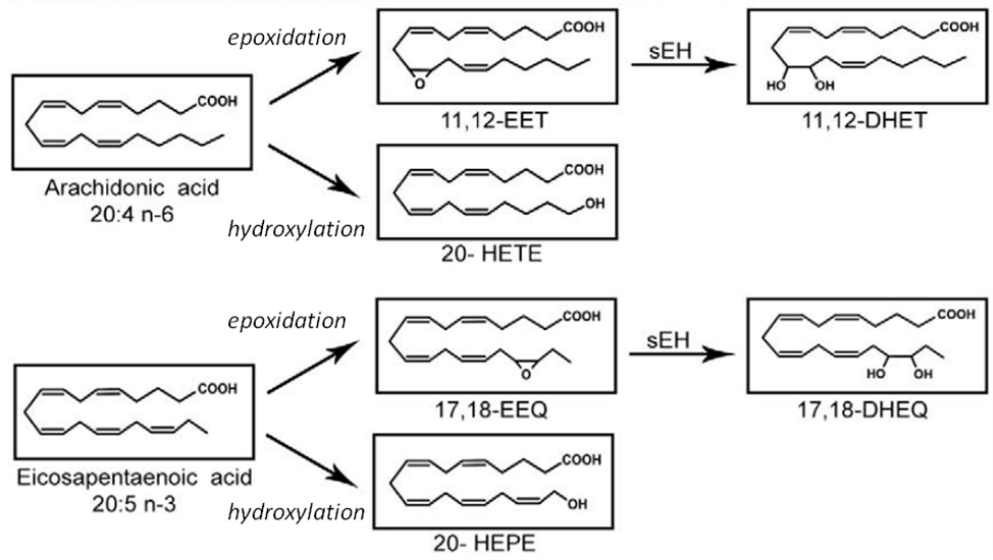
COX = cyclooxygenase; LOX = lipoxygenase; LT = leukotriene; PG = prostaglandin; TX = thromboxane R_v = resolving

Figure 4 Chain Elongation and Desaturation Enzymes are Responsible for Interconversion between EPA, DPA and DHA, All of Which Undergo β-oxidation



EPA = eicosapentaenoic acid; DPA = docosapentaenoic acid; DHA = docosahexaenoic acid

Figure 5 Cytochrome P450-Dependent Metabolism of AA and EPA



AA = arachidonic acid; CYP = cytochrome P450; DHEQ = dihydroxyeicosaquatraenoic acid; DHET = dihydroxyeicosatrienoic acid; EEQ = epoxyeicosatetraenoic acid; EET = epoxyeicosatrienoic acid; EPA = eicosapentaenoic acid; HEPE = hydroxyeicosapentaenoic acid; HETE = hydroxyeicosatetraenoic acid; sEH = soluble epoxide hydrolase.

CYP-mediated metabolism is a minor pathway of elimination of EPA, the potential of EPA to inhibit or induce CYP isoforms was investigated. The potential of EPA to inhibit a series of CYP isoforms was evaluated using human liver microsomes (Study AMR-NC-11-01). EPA was a weak inhibitor *in vitro* of CYP2C19, CYP2C9, and CYP2C8, even less so for CYP2B6 and CYP3A, with virtually no inhibition of CYP1A2, CYP2D6, and CYP2E1. There was no substantial evidence of time-dependent (mechanism-based) inhibition of EPA. The sponsor conducted clinical DDI studies (Study AMR-01-01-0020, Study AMR-01-01-0021, and Study AMR-01-01-0023) to assess the potential for clinically significant interactions with CYP2C19, CYP2C9, CYP2C8, and CYP3A4 substrates.

A study in cultured human hepatocytes suggests that EPA has a low potential to induce the activities of CYP3A, CYP2C9, and CYP1A2 (Study AMR-NC-11-02). Clinical pharmacology studies to assess potentially clinically significant induction of these isoforms were not performed.

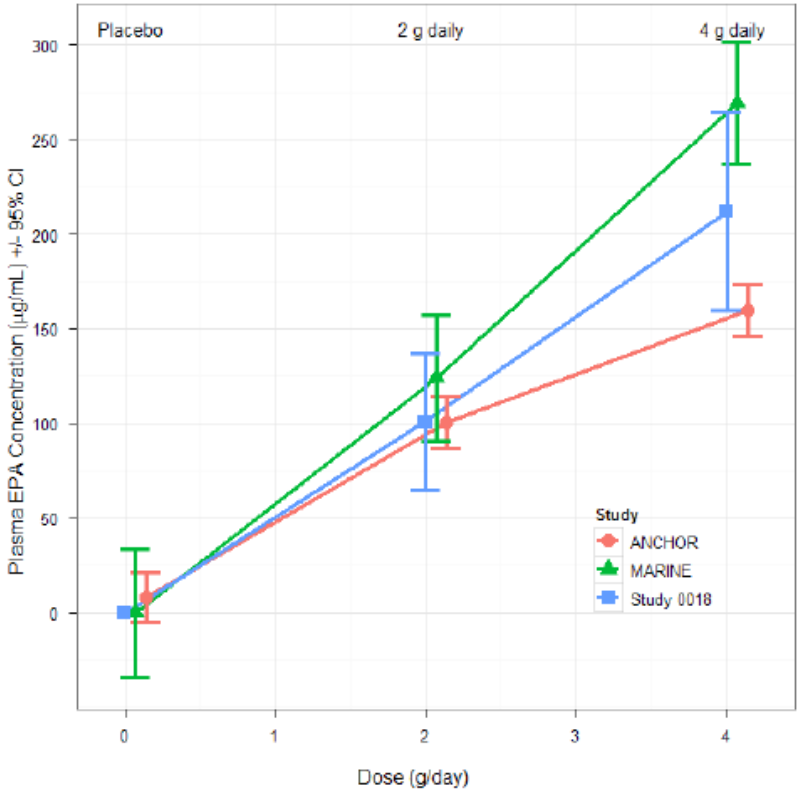
2.2.5.7 What are the characteristics of drug excretion?

After ingestion of ethyl-EPA, the compound is completely hydrolyzed and converted into EPA by pancreatic lipase in the small intestine. The major pathway of elimination of EPA is β-oxidation. The end products are carbon dioxide (CO_2) and water, principally excreted in expired breath.

2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

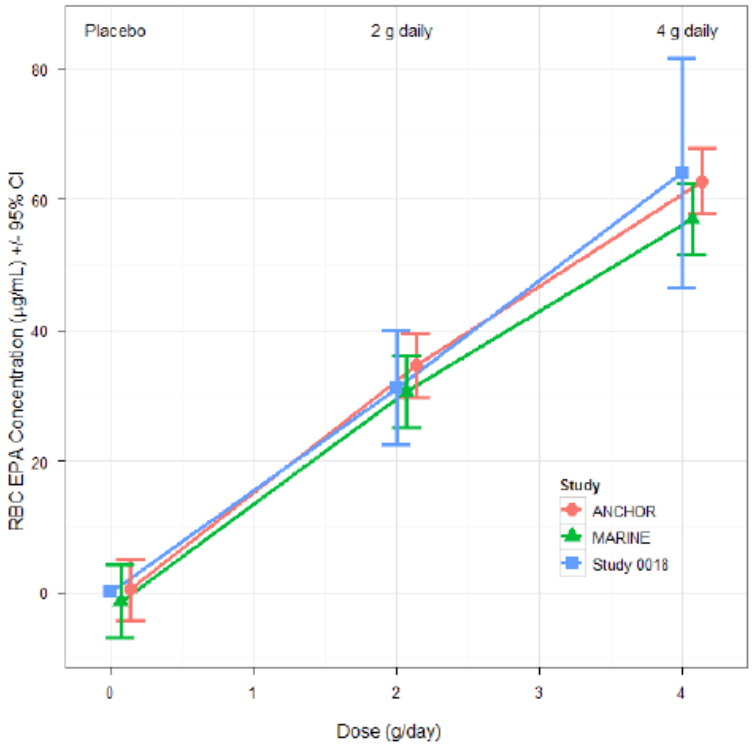
Trough EPA concentration data from repeated BID doses of ethyl-EPA in healthy volunteers (28 days of dosing) and in patients with hypertriglyceridemia (12 weeks of dosing) indicate that EPA systemic exposure increased with dose in plasma (Figure 6) and in RBCs (Figure 7). The relationship between EPA concentrations and dose are similar between healthy volunteers and patients.

Figure 6 Mean Plasma Trough EPA Concentrations (95% CI) by Dose in Healthy Volunteers (Study AMR-01-01-0018) and in Patients with Hypertriglyceridemia (MARINE and ANCHOR Studies)



- 95% CI = 95% Confidence Interval
- MARINE = Study AMR-01-01-0016; ANCHOR = Study AMR-01-01-0017
- Mean concentrations are based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state measured with a validated liquid chromatography/tandem mass spectrometry assay.
- In Study 0018 (Protocol AMR-01-01-0018), in healthy volunteers, the trough EPA concentrations were measured after 28 days of dosing with 2 or 4 g/day Vascepa (there was no placebo group but a value of zero is plotted as a point of reference). In the MARINE and ANCHOR studies, in patients with very high and high baseline triglyceride levels, respectively, the trough EPA concentrations were measured after 12 weeks of dosing with placebo, 2 g/day Vascepa or 4 g/day Vascepa.
- Baseline EPA concentrations & number of subjects:
    - Study 0018: 5.68(2 g/day, N=10), 12.1 (4 g/day, N=9) µg/mL
    - MARINE: 14.7 (placebo, N=64), 15.7 (2 g/day, N=61), 16.0 (4 g/day, N=66) µg/mL
    - ANCHOR: 11.2 (placebo, N=79), 10.9 (2 g/day, N=71), 11.6 (4 g/day, N=69) µg/mL

Figure 7 Mean RBC Trough EPA Concentrations (95% CI) by Dose in Healthy Volunteers (Study AMR-01-01-0018) and in Patients with Hypertriglyceridemia (MARINE and ANCHOR Studies)



- 95% CI = 95% Confidence Interval; RBC = Red Blood Cells
- MARINE = Study AMR-01-01-0016; ANCHOR = Study AMR-01-01-0017
- Mean concentrations are based on baseline-subtracted trough concentrations of total EPA (change from baseline) at steady state measured with a validated liquid chromatography/tandem mass spectrometry assay.
- In Study 0018 (Protocol AMR-01-01-0018), in healthy volunteers, the trough EPA concentrations were measured after 28 days of dosing with 2 or 4 g/day Vascepa (there was no placebo group but a value of zero is plotted as a point of reference). In the MARINE and ANCHOR studies, in patients with very high and high baseline triglyceride levels, respectively, the trough EPA concentrations were measured after 12 weeks of dosing with placebo, 2 g/day Vascepa or 4 g/day Vascepa.
- Baseline EPA concentrations & number of subjects:
    - Study 0018: 5.68(2 g/day, N=10), 12.1 (4 g/day, N=9) µg/mL
    - MARINE: 14.7 (placebo, N=64), 15.7 (2 g/day, N=61), 16.0 (4 g/day, N=66) µg/mL
    - ANCHOR: 11.2 (placebo, N=79), 10.9 (2 g/day, N=71), 11.6 (4 g/day, N=69) µg/mL

2.2.5.9 How do the PK parameters change with time following chronic dosing?

T_{max} did not change while exposure increased following chronic doing, change of drug clearance was not adequately evaluated.

2.3 INTRINSIC FACTORS

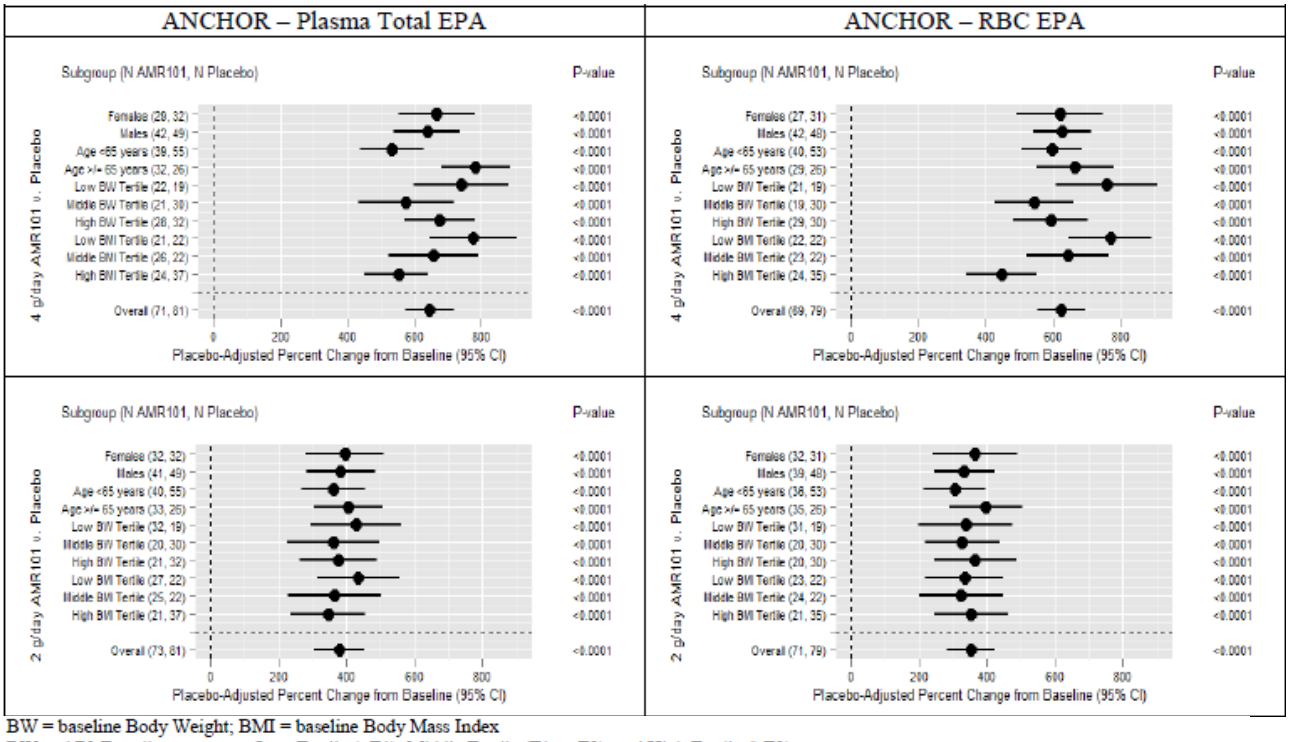
2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1 Age

In a PK study in healthy male and female volunteers (Study AMR-01-01-0018) after 28 days of dosing with 2 and 4 g/day ethyl-EPA, no effect of age (20-55 years) was observed on the AUC and C_{max} of total and unesterified plasma EPA concentrations (see 4.2 Individual Study Review).

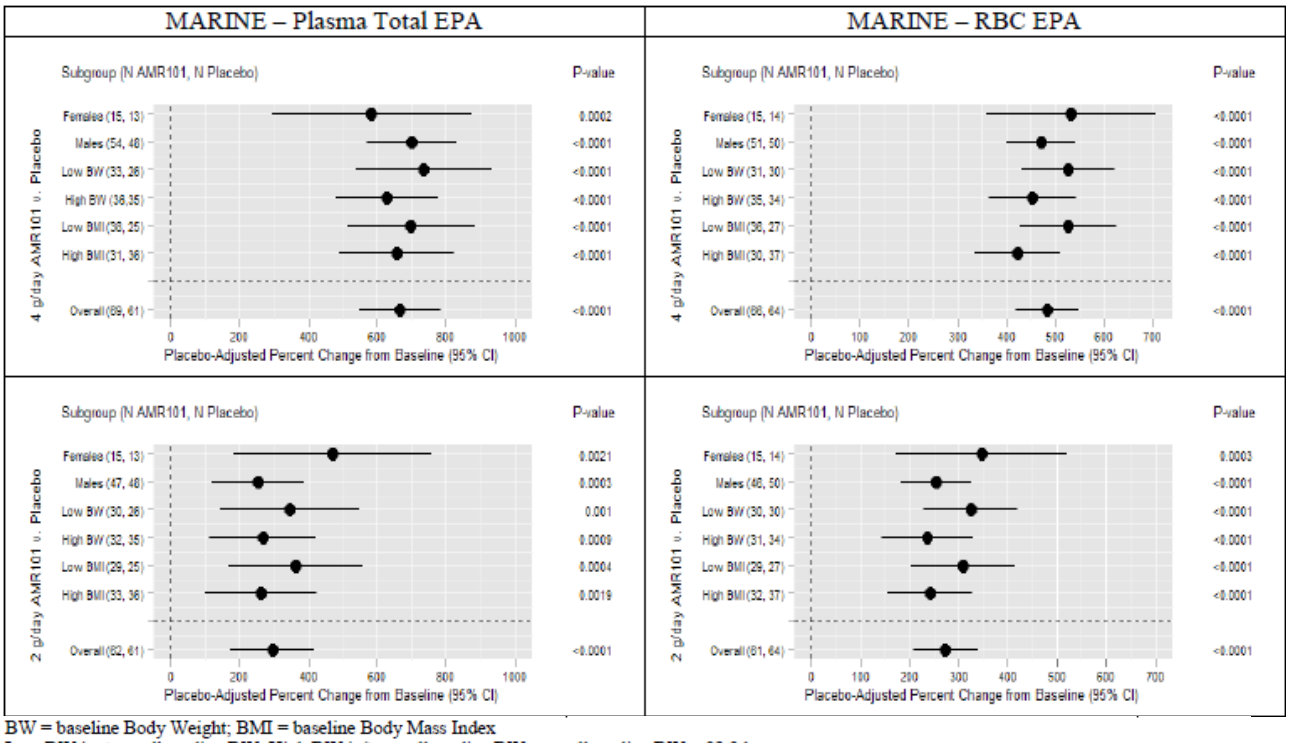
In the MARINE study, subgroup analyses by age were not meaningful due to the small number of patients over the age of 65 years (only 18 patients were >65 years of age). In the ANCHOR study, 702 adult patients at high risk of CVD with persistent high fasting triglyceride levels (≥200 mg/dL and <500 mg/dL) were recruited. At 4 g/day dose, the median and standard deviation of age is 62 and 10.0 years, respectively with minimum age being 31 years and maximum age being 85 years. At this dose level, 32 geriatric patients showed higher exposure than the 39 patients who were younger than 65 years old. The clinical significance of increased exposure in patients ≥65 years at the 4 g/day dose is unknown. However, at 2 g/day dose, plasma total EPA exposure were not significantly different between these two age groups (33 patients ≥65 and 40 patients <65 years) (Figure 8). The median and SD of age at the 2 g/day dose is 62 and 9.4 years, minimum age is 31 years and maximum age is 84 years. With the ANCHOR study patient population not being the target population for the claimed indication and with inconsistent findings between the two dose levels, it's inconclusive if geriatric patients will have increased plasma EPA exposure of clinical relevance.

Figure 8 Plasma and RBC EPA Trough Concentrations in Subgroups of Gender, Age, Body Weight and Body Mass Index - Mean Percent Change from Baseline at Week 12 (95% CI) of Ethyl-EPA vs. Placebo (ANCHOR)



BW = baseline Body Weight; BMI = baseline Body Mass Index
BW and BMI tertile groups are: Low Tertile (<T1), Middle Tertile (T1 - <T2), and High Tertile (≥T2).
For BW: T1= 86.3 kg; T2 = 103.6 kg. For BMI: T1= 30 kg/m^2; T2 = 35 kg/m^2.
EPA concentrations (total EPA) were measured with a validated liquid chromatography/tandem mass spectrometry assay.
The Least Squares Mean, 95% CI (95% Confidence Interval) and P-values are from ANCOVAs. The ANCOVA model included treatment, gender, type of statin, and presence of diabetes as factors and the baseline EPA concentration value as a covariate.

Figure 9 Plasma and RBC EPA Trough Concentrations in Subgroups of Gender, Body Weight and Body Mass Index - Mean Percent Change from Baseline at Week 12 (95% CI) of Vascepa vs. Placebo (MARINE)



BW = baseline Body Weight; BMI = baseline Body Mass Index
Low BW is <overall median BW; High BW is ≥overall median BW; overall median BW = 92.3 kg
Low BMI is <overall median BMI; High BMI is ≥overall median BMI; overall median BMI = 30.6 kg/m2.
EPA concentrations (total EPA) were measured with a validated liquid chromatography/tandem mass spectrometry assay.
The Least Squares Mean, 95% CI (95% Confidence Interval) and P-values are from ANCOVAs. The ANCOVA model included treatment, gender, and the use of statin therapy at randomization as factors and the baseline EPA concentration value as a covariate.

Pediatric patients: ethyl-EPA has not been studied in pediatric patients.

2.3.1.2 Gender

In Study AMR-01-01-0018, after 28 days of dosing with 2 and 4 g/day ethyl-EPA, EPA C_{min} values appeared to be slightly lower in males than in females in some treatment groups, but overall, no consistent gender effect was observed based on all remaining exposure parameters (AUC and C_{max}).

Increases (percent change from baseline at Week 12 versus placebo) in trough EPA concentrations (total EPA) in plasma and RBCs were similar in hypertriglyceridemic patients in MARINE (Figure 9) and in ANCHOR (Figure 8).

2.3.1.3 Renal impairment

Ethyl-EPA does not undergo renal excretion; studies investigating the effect of renal insufficiency on the PK of ethyl-EPA were not performed.

2.3.1.4 Hepatic impairment

Hepatic clearance is a minor pathway of ethyl-EPA elimination; studies investigating the effect of hepatic insufficiency on the PK of ethyl-EPA were not performed.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

No dosage regimen adjustment is recommended.

2.4 EXTRINSIC FACTORS

2.4.1 Drug-drug interactions

2.4.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. A standard battery of 8 CYPs (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A) was tested *in vitro* for inhibition potential of EPA. The following CYP isoforms indicated a possible DDI (in decreasing order of potential): 2C19, 2C9, 2C8, 2B6, and 3A, because their ratio of C_{max}/IC_{50} exceeded 0.1.

2.4.1.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

No.

2.4.1.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Yes, EPA is a weak inhibitor of CYP2C19, 2C9, 2C8, 2B6, and 3A. A study in cultured human hepatocytes suggests that EPA has a low potential to induce the activities of CYP3A, CYP2C9, and CYP1A2 (Study AMR-NC-11-02). Clinical pharmacology studies to assess potentially clinically significant induction of these isoforms were not performed.

2.4.1.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

No.

2.4.1.5 Are there other metabolic/transporter pathways that may be important?

Yes, see section 2.2.5.6.

2.4.1.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No.

2.4.1.7 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.2 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Not applicable.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-market formulation was used in the pivotal clinical trial.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

No food effect studies were performed, ethyl-EPA was administered with or following a meal in all clinical studies and was directed to be administered with food in the label.

2.5.4 Are the commercial and clinical formulations used during development adequately linked?

The commercial formulation was used in the submitted studies.

2.6 ANALYTICAL SECTION

Over the course of the development of Vascepa, three assays were used for the determination of EPA concentrations in human biomatrix samples:

• A gas chromatography plus flame ionization detector (GC/FID) assay method was developed to measure total EPA (which measures the sum of unesterified and esterified EPA) and 27 other fatty acids, in plasma and RBCs from clinical studies in support of Amarin's CNS program. Study LA01.01.009 used this assay method.

• A second assay was developed utilizing separation by HPLC and detection by tandem mass spectrometry (LC/MS-MS assay) to measure unesterified EPA in human plasma in the clinical studies of Amarin's hypertriglyceridemia program. This assay was also used in support of the nonclinical development program (validated for mouse, rat and dog plasma).

• A third assay, an LC/MS-MS assay, was developed to measure total EPA in plasma and RBCs in the clinical studies of the hypertriglyceridemia program, including PK studies in healthy volunteers and in the hypertriglyceridemic patients in the Phase 3 trials. This assay is considered the principal PK assay.

An LC/MS-MS assay was also developed to measure the parent drug, ethyl-EPA, in a limited number of plasma samples after ethyl-EPA administration.

The LC/MS-MS assay performance characteristics are summarized in Table 6, while the by-study performance characteristics of assays used to support phase 1 to 3 clinical studies are summarized in Table 7.

Table 6 Validation Reports and Assay Characteristics of the LC/MS-MS Assays for Measuring EPA and Ethyl-EPA Concentrations in Plasma and RBC Samples

Study Number/ Report Number	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
Test Facility Study No. 310873, Report No. 32160	Validation of an Analytical Method for the Determination of Total Eicosapentaenoic Acid (EPA) in Human Plasma and Erythrocytes by LC/MS-MS	(b) (4)	Plasma	Total EPA 10-1000 µg/mL	Total EPA 10 µg/mL	Total EPA 95.2% to 103.0% at 10-1000 µg/mL	Total EPA 3.6% to 7.3% at 10-1000 µg/mL
			RBC	Total EPA 5-500 µg/mL	Total EPA 5 µg/mL	Total EPA 98.4% to 102.0% at 5-500 µg/mL	Total EPA 2.6% to 7.0% at 5-500 µg/mL
Test Facility Study No. 311369, Report No. 31687	Validation of an Analytical Method for the Determination of Un-esterified Eicosapentaenoic Acid (EPA) in Human Plasma by LC/MS-MS		Plasma	Unesterified EPA 50-5000 ng/mL	Unesterified EPA 50 ng/mL	Unesterified EPA 95.2% to 102.6% at 50-5000 ng/mL	Unesterified EPA 2.2% to 5.8% at 50-5000 ng/mL
Test Facility Study No. 313125, Report No. 32408	Qualification of an Analytical Method for the Determination of Eicosapentaenoic Acid Ethyl Ester (Ethyl-EPA) in Plasma Samples from Clinical Study Nos. AMR-01-01-0016, AMR-01-01-0017 and AMR-01-01-0018 [LC/MS-MS Method]		Plasma	Ethyl-EPA 50-5000 ng/mL	Ethyl-EPA 50 ng/mL	Ethyl-EPA 95.5% to 105.0% at 50 -5000 ng/mL	Ethyl-EPA 1.9% to 8.8% at 50 to 5000 ng/mL

RBC = red blood cell; LLOQ = lower limit of quantitation

Table 7 Assay Performance Results from Measuring EPA Concentrations in Plasma and RBCs from Clinical Studies with Ethyl-EPA.

Study Number/ Assay Method	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
LA01.01.009 GC/FID 28 fatty acids (including EPA)	A Phase I Multiple Dose Pharmacokinetic Study Of LAX-101 in Healthy Male Volunteers	(b) (4)	Plasma	5-1000 µg/g	3 µg/g	Repeatability: 6% relative standard deviation (RSD) over the range of 75%-125%	Not available (not possible to obtain standards of high enough purity of every fatty acid determined)
			RBC	5-500 µg/g	3 µg/g	6% RSD over the range of 75%-125%	
Test Laboratory Reference No. 311416, Phase Report No. 31690 Sponsor's Clinical Study No. AMR-01-01-0018 LC/MS-MS	Determination of Total Eicosapentaenoic Acid (EPA) in Plasma and Erythrocyte Samples and Un-Esterified EPA in Plasma Samples From Healthy Volunteers in a Clinical Study (Clinical Study No. AMR-01-01-0018) by LC/MS-MS (Randomized, Open-Label, Multiple-Dose, Parallel, Comparative, Pharmacokinetic Study in Healthy Subjects After Oral Administration of Vascepa 500 mg or AMR 1000 mg Capsules)		Plasma	Total EPA 10-1000 µg/mL	Total EPA 10 µg/mL	Total EPA 97.9% to 103.0% at 10-1000 µg/mL	Total EPA 3.3% to 8.5% at 10-1000 µg/mL
			Plasma	Unesterified EPA 50-5000 ng/mL	Unesterified EPA 50 ng/mL	Unesterified EPA 95.6% to 105.6% at 50 -5000 ng/mL	Unesterified EPA 2.9% to 8.0% at 50 to 5000 ng/mL
			RBC	Total EPA 5-500 µg/mL	Total EPA 5 µg/mL	Total EPA 98.8% to 101.4% at 5-500 µg/mL	Total EPA 3.8% to 7.8% at 5-500 µg/mL
Test Laboratory Reference No. 312619, Phase Report No. 32174 LC/MS-MS	Determination of Eicosapentaenoic Acid (EPA) in Plasma Samples from a Clinical Study (Clinical Study No. AMR-01-01-0020-Open-Label, Cross-Over, Drug-Drug Interaction Study Between Vascepa and Omeprazole and Between Vascepa and Rosiglitazone in Healthy Subjects)		Plasma	Total EPA 10-1000 µg/mL	Total EPA 10 µg/mL	Total EPA 87.2% to 106.5% at 10-1000 µg/mL	Total EPA 4.6% at 25 µg/mL 4.5% at 100 µg/mL 5.9% at 800 µg/mL
			Plasma	Unesterified EPA 50-5000 ng/mL	Unesterified EPA 50 ng/mL	Unesterified EPA 93.6% to 112.4% at 50-5000 ng/mL	Unesterified EPA 6.7% at 125 ng/mL, 4.8% at 1000 ng/mL, 4.0% at 4000 ng/mL

Study Number/ Assay Method	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
Test Facility Study No. 312954, Report No. 32413 LC/MS-MS	Determination of Eicosapentaenoic Acid (EPA) in Plasma Samples From a Clinical Study (Clinical Study No. AMR-01-01-0021) Open-Label, Cross-Over, Drug-Drug Interaction Study Between Vascepa and Warfarin in Healthy Subjects	(b) (4)	Plasma	Total EPA 10–1000 µg/mL	Total EPA 10 µg/mL	Total EPA 87.2% to 106.0%	Total EPA 1.9% to 5.8%
				Unesterified EPA 50–5000 ng/mL	Unesterified EPA 50 ng/mL	Unesterified EPA 93.8% to 103.5%	Unesterified EPA 0.6% to 4.9%
Test Facility Study No. 312980, Report No. 32412 LC/MS-MS	Determination of Eicosapentaenoic Acid (EPA) in Plasma Samples from a Clinical Study (Clinical Study No. AMR-01-01-0023: A Phase 1, Open-Label, Crossover, Drug-Drug Interaction Study between Vascepa and Atorvastatin in Healthy Subjects		Plasma	Total EPA 10–1000 µg/mL	Total EPA 10 µg/mL	Total EPA 86.9% to 111.0%	Total EPA 1.9% to 11.6%
				Unesterified EPA 50–5000 ng/mL	Unesterified EPA 50 ng/mL	Unesterified EPA 93.0% to 113%	Unesterified EPA 2.8% to 6.0%

Study Number/ Assay Method	Study Title	Analytical Laboratory	Sample Matrix	Assay Range	LLOQ	Accuracy	Precision
AMR-01-01-016 CSR (MARINE) LC/MS-MS	Determination of Total Eicosapentaenoic Acid (EPA) in Plasma and Erythrocyte Samples from Patients in the Double Blind Phase of a Clinical Study by LC/MS-MS (A Phase 3, Multicenter, Placebo-Controlled, Randomized, Double Blind, 12-Week Study with an Open-Label Extension to Evaluate the Efficacy and Safety of in Patients with Fasting Triglyceride Levels ≥500 mg/dL and ≤2000 mg/dL: The Vascepa MARINE Study)	(b) (4)	Plasma	Total EPA 10-1000 µg/mL	Total EPA 10 µg/mL	Total EPA 95.0% to 103.0% at 10-1000 µg/mL	Total EPA 3.4% to 7.9% at 10-1000 µg/mL
			RBC	Total EPA 5-500 µg/mL	Total EPA 5 µg/mL	Total EPA 96.4% to 105.0% at 5-500 µg/mL	Total EPA 2.0% to 9.3% at 5-500 µg/mL
Test Laboratory Reference No. 311374, Phase Report No. 32051 Clinical Study No. AMR-01-01-0017 (ANCHOR) LC/MS-MS	Determination of Total Eicosapentaenoic Acid (EPA) in Plasma and Erythrocyte Samples From Patients in a Clinical Study (Clinical Study No. AMR-01-01-0017) by LC/MS-MS (A Phase 3, Multi-Center, Placebo Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of Vascepa on Fasting Serum Triglyceride Levels in Patients with Persistent High Triglyceride Levels (≥200 mg/dL and <500 mg/dL) Despite Statin Therapy: The Vascepa ANCHOR Study)		Plasma	Total EPA 10-1000 µg/mL	Total EPA 10 µg/mL	Total EPA 97.1% to 105.0% at 10-1000 µg/mL	Total EPA 4.2% to 8.8% at 10-1000 µg/mL
			RBC	Total EPA 5-500 µg/mL	Total EPA 5 µg/mL	Total EPA 97.0% to 104.2% at 5-500 µg/mL	Total EPA 3.1% to 8.8% at 5-500 µg/mL

3 DETAILED LABELING RECOMMENDATIONS

Recommended changes by this reviewer are indicated by strikethrough for deleted text and additions by underlined text, as follows:

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------DOSAGE AND ADMINISTRATION----------

The daily dose of VASCEPA is 4g/day taken as two 1 gram capsules twice daily (BID) with food. (b) (4) (2)

----------DRUG INTERACTIONS----------

(b) (4) Omega-3-acids may prolong bleeding time. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.(7, (b) (4))

2 DOSAGE AND ADMINISTRATION

The daily dose of VASCEPA is 4 g/day taken as two 1 gram capsules twice daily (BID) with food. (b) (4)

7 DRUG INTERACTIONS

7.1 Anticoagulants

(b) (4)

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in those studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.

(b) (4)

12.3 Pharmacokinetics

Absorption: After oral administration, VASCEPA is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of VASCEPA.

Vascepa was administered with or following a meal in all clinical studies, no food effect studies were performed. Take Vascepa with or following a meal.

Distribution: The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Metabolism& Excretion: EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA. The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hr. VASCEPA does not undergo renal excretion.

Drug-Drug Interactions

VASCEPA was studied at the 4 g/day dose level with the following medications which are typical substrates of cytochrome P450 enzymes, and no significant drug-drug interactions were observed:

Omeprazole: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of omeprazole when co-administered at 40 mg/day to steady-state.

Rosiglitazone: In drug-drug interaction study with 28 healthy adult subjects, VASCEPA

4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of rosiglitazone at 4 mg.

Warfarin: In a drug-drug interaction study with 25 healthy adult subjects, VASCEPA 4 g/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 warfarin (b) (4) when co-administered as racemic warfarin at 25 mg.

Atorvastatin: In a drug-drug interaction study of 26 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of atorvastatin, 2 hydroxyatorvastatin, or 4 hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day to steady-state.

(b) (4)

Gender: When administered VASCEPA in clinical trials, plasma total EPA concentrations did not differ significantly between men and women.

Geriatric: In a clinical study of 702 adult patients at high risk of CVD, with persistent high fasting triglyceride levels (≥200 mg/dL and <500 mg/dL) [the ANCHOR study], plasma total EPA trough concentrations were evaluated. At 4 g/day dose, 32 geriatric patients showed higher exposure than 39 patients who were younger than 65 years old. However, at 2 g/day dose, plasma total EPA exposure was not significantly different between these two age groups (33 patients ≥65 and 40 patinets <65 years). The clinical significance of this is unknown.

Pediatric: The pharmacokinetics of VASCEPA have not been studied in pediatric patients.

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

4 APPENDICES

4.1 PROPOSED PACKAGE INSERT (ORIGINAL AND ANNOTATED)

See attached draft annotated label at the end of this document.

4.2 INDIVIDUAL STUDY REVIEW

4.2.1 LA01.01.0009: Pharmacokinetic Study of Vascepa in Healthy Male Volunteers after Oral Administration of 0.5 g Vascepa Capsules at Doses of 2 g/day

Objectives:

The primary objectives of the study are as follows:

• To determine the pharmacokinetic profiles over a 48 hour period of a single oral dose of ethyl-EPA followed by multiple oral doses (once and twice daily) in healthy, male subjects.

• To determine the safety and tolerability of a single oral dose of ethyl-EPA followed by multiple oral doses (once and twice daily) in healthy, male subjects.

The secondary objective of the study is to explore any differences in pharmacokinetic profile between once and twice daily dosing.

Study design:

This was a Phase 1, single-center, open-label, randomized, single and multiple dose, PK study of ethyl-EPA in 24 healthy males. Healthy subjects were allocated to two dose groups of 12 subjects each. Both groups received the same total daily dose of ethyl-EPA, as a soft gelatin 0.5 g capsule, but the dosing regimens were different. All subjects received a single oral dose of 2 g ethyl-EPA immediately after a standard breakfast on Day 1. After a one-day washout (Day 2), Treatment Group A received 28 continuous QD doses of 2 g ethyl-EPA (Days 3 to 30); whereas Treatment Group B received 27 continuous BID doses of 1 g ethyl-EPA (Days 3 to 29) and a single dose of 2 g ethyl-EPA on Day 30. Ethyl-EPA was administered immediately after meals.

PK evaluations:

The primary pharmacokinetic analysis variable is the concentration of EPA in plasma. Blood samples for pharmacokinetic analysis were taken at the following time points for Treatment Groups A and B:

• Days 1 and 30: Pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 h postdose
• Days 9, 16, 23: Pre morning dose
• Days 37, 44, 58: Post last dose

Study results:

Twenty-one subjects completed the study: 10 in Group A and 11 in Group B. Total EPA concentrations were measured with the GC/FID method. Due to a freezer malfunction, some blood samples were lost. As a result, Group A blood samples were limited to the predose times on Days 1, 9, 16, 23, and 30 and after dosing (last dose on Day 30) on Days 37, 44, and 58; while Group B samples included the complete Days 1 and 30 sampling (predose to 48 hr) only. Hence, single-dose and repeated-dose PK profiles were based on Group B samples, while the time course of accumulation was based on Group A samples.

As shown in Table 8, a single oral dose of 2 g ethyl-EPA resulted in a slow rise in plasma EPA concentrations. Maximum values were observed 5 hours after dosing, with EPA concentrations remaining above baseline 48 hours after administration. The sponsor reported a terminal half-life of EPA from plasma of 87 hr (not baseline adjusted) or 42 hr (baseline adjusted). However, due to the limited sampling time points (48 hours), the estimation of half life, $AUC_{0-\infty}$ etc. are unreliable.

Table 8 Pharmacokinetic Parameters Based on Total EPA Concentrations in Plasma Following a Single Dose of 2 g Ethyl-EPA (Day 1) in Male Volunteers (Group B)

Baseline Adjusted	λ_z (hr^{-1})	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (µg/g)	AUC_{0-48hr} (µg*hr/g)	$AUC_{0-\infty}$ (µg*hr/g)	V_z/F (L)	CL/F (mL/hr)
No	0.010 (0.004)	86.6 (65.4)	4.64 (0.92)	78.3 (33.7)	2299 (972)	7615 (5251)	37.0 (13.2)	381 (202)
Yes	0.021 (0.009)	42.2 (30.9)	4.64 (0.92)	55.5 (28.2)	1206 (617)	2375 (1615)	58.8 (23.9)	1270 (830)

Values expressed as mean (SD) of N=11 subjects.
EPA concentrations were measured with a GC/FID assay.
Source: Study LA01.01.0009 CSR Addendum 16 June 2004

Accumulation of EPA was evident after QD dosing since a higher exposure was observed on Day 30 compared after the single dose on Day 1, as measured by C_{max} (Table 9). Predose plasma concentrations on Days 9, 16, 23, and 30 were comparable, suggesting that steady state was largely attained by Day 9 (Figure 10).

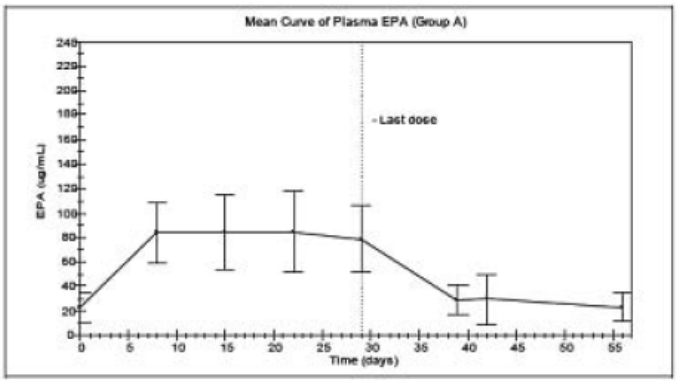
Table 9 Pharmacokinetic Parameters Based on Total EPA Concentrations in Plasma Following a Single 2 g Ethyl-EPA Dose on Day 30 After Repeated BID Doses of 1 g Ethyl-EPA(2 g/day) in Male Volunteers (Group B)

Baseline Adjusted	T_{max} (hr)	C_{max} (µg/g)	C_{min} (µg/g)	AUC_τ (µg*hr/g)	CL/F (mL/hr)
No	4.82 (2.52)	175 (52.6)	106 (23.7)	1631 (445)	1316 (374)
Yes	4.82 (2.52)	152 (44.5)	83.7 (15.6)	1358 (340)	1569 (440)

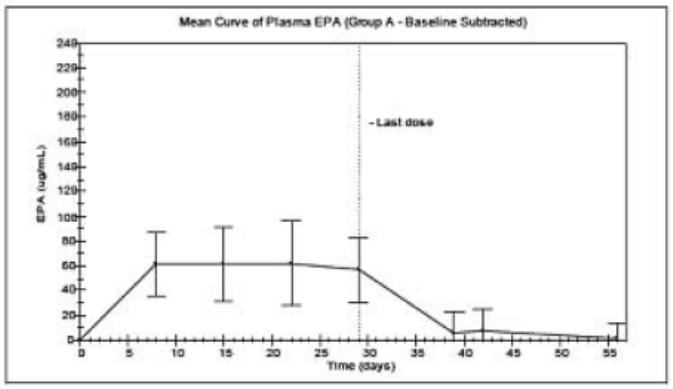
Values expressed as mean (SD) of N=11 subjects.
EPA concentrations were measured with a GC/FID assay.
Source: Study LA01.01.0009 CSR Addendum 16 June 2004

Figure 10 Trough Plasma EPA Concentrations (SD) following Repeated BID Administration of 2 g/day Ethyl-EPA in Male Volunteers (Group A)

(A) Not Baseline Adjusted



(B) Baseline Adjusted



Source: Study LA01.01.0009 CSR 16 June 2004
N= 10 subjects

4.2.2 AMR-01-01-0018: Pharmacokinetic Study in Healthy Male and Female Volunteers after Oral Administration of 1 g or 0.5 g Ethyl-EPA Capsules at Doses of 2 and 4 g/day

Objectives:

• To characterize the pharmacokinetics (PK) of EPA in plasma and red blood cells after multiple dose oral administration of ethyl-EPA for 28 days.
• To compare the PK of EPA after multiple dose oral administration of vascepa 1000 mg capsules and vascepa 500 mg capsules.
• To compare the PK of EPA after multiple dose oral administration of vascepa 2 g/day and 4 g/day.
• To compare the PK of EPA after once-per-day versus twice-per-day dosing of vascepa 2 g/day.
• To compare the PK of EPA between males and females.

Study design:

This was a Phase 1, single-center, open-label, randomized, multiple-dose, parallel (one-period), comparative PK study with ethyl-EPA in healthy male and female subjects. Forty-eight subjects (12 per treatment group, with 6 male and 6 female subjects in each group) were randomized to

receive:

• Group 1: ethyl-EPA 1 g BID (1 g capsule)
• Group 2: ethyl-EPA 2 g BID (1 g capsule)
• Group 3: ethyl-EPA 2 g QD (1 g capsule)
• Group 4: ethyl-EPA 1 g BID (500 mg capsules)

This study consisted of the following study periods:

• Screening Period (14 days): to evaluate subject eligibility;
• Treatment Period (28 days): subjects received study drug during the planned visits or self-administered the study drug while away from the study site. During the visits, study procedures were performed for evaluation of safety and pharmacokinetics;
• Post-Treatment PK Sampling Period (18 days): visits spread over 18 days during which study procedures were performed for evaluation of safety and pharmacokinetics.

Blood samples for the determination of total EPA concentrations in plasma and RBCs, and of unesterified EPA concentrations in plasma were obtained before the morning dose on Days 1, 14, 26, and 28, and up to 432 hours (18 days) after the morning dose on Day 28.

Primary Pharmacokinetic Endpoint:
$AUC_{0\text{-}24hr}$, the area under the plasma total EPA concentration versus time curve over 24 hours on Day 28 was calculated as follows:

• Groups 1, 2, and 4 (twice daily dosing regimens): two times the AUC from time zero to 12 hours (2 x $AUC_{0\text{-}12hr}$) calculated from the concentration-time curve on Day 28 (0-12 hr after the last dose).
• Group 3 (once daily dosing regimen): the $AUC_{0\text{-}24hr}$ calculated from the concentration-time curve on Day 28 (24 hr after the last dose).

All AUCs were calculated using the linear trapezoidal rule.

Secondary Pharmacokinetic Endpoints:
• $AUC_{0\text{-}24hr}$ for unesterified EPA concentrations in plasma on Day 28, and total EPA concentrations in RBCs on Day 28 (calculated the same as the primary PK endpoint).
• C_{max}, T_{max}, C_{min}, $T_{1/2}$, CL/F, and Vz/F based on total and unesterified EPA concentrations in plasma after the last dose (Day 28).
• C_{max}, T_{max}, C_{min}, and $T_{1/2}$ based on total EPA concentrations in RBCs (Day 28).
• C_{min} (trough EPA concentrations) of total and unesterified EPA concentrations in plasma and total EPA concentrations in RBCs on Days 14, 26, and 28.

Pharmacokinetic Analyses:

All PK parameters except T_{max} and $T_{1/2}$ were log-transformed before statistical comparisons among treatment groups and gender. All PK parameters except T_{max} were log-transformed and analyzed using mixed effect ANOVA modeling that included treatment and gender as fixed effects and subject as a random effect to investigate the effects of treatment and gender. The geometric means of PK parameters for each treatment group are reported. Point estimates and

90% confidence intervals (CI) for the ratios of geometric means for pair-wise comparisons are provided. Values of T_{max} were compared among groups with the Wilcoxon Rank Sum test, and each median difference and associated 90% CI estimated using the method of Hodges-Lehmann.

Statistical comparisons among treatment groups were performed on the PK data for the primary and secondary endpoints as follows:

EPA exposure (AUC and C_{max}) was compared with and without baseline subtraction between Treatment Groups 1 and 3 for comparison of once-per-day versus twice-per-day dosing. Statistical comparison of log-transformed AUC and C_{max} data for Treatment Group 1 and Treatment Group 3 was performed using the mixed effect ANOVA modeling with correction for gender. Least square means and associated 90% CIs and p-values were generated.

EPA exposure (AUC and C_{max}) was compared with and without baseline subtraction between Treatment Groups 1 and 4 for comparison of formulations. Statistical comparison of log-transformed AUC and C_{max} data for Treatment Group 1 and Treatment Group 4 was performed using the mixed effect ANOVA modeling with correction for gender. Least square means and associated 90% CIs and p-values were generated.

Dose-normalized AUC and C_{max} values (AUC and C_{max} divided by the dose) were compared with and without baseline subtraction between Treatment Groups 1 and 2. Statistical comparison of logtransformed dose-normalized AUC and C_{max} data for Treatment Group 1 and Treatment Group 2 was performed using the mixed effect ANOVA modeling with correction for gender. Least square means and associated 90% CIs and p-values were generated.

Trough plasma EPA concentrations (C_{min}) on Days 14, 26 and 28 were compared to evaluate whether steady state was reached by Day 28.

Study results:

Forty-two subjects completed the study: 10 in Group 1, 9 in Group 2, 11 in Group 3, and 12 in Group 4.

Oral doses of 2 g/day and 4 g/day of ethyl-EPA resulted in maximum plasma concentrations of total EPA approximately 5 hours after dosing (Figure 11, Table 10). The mean terminal half-life of total EPA in plasma was long, ranging between 75 and 89 hours based on baseline-adjusted concentrations and between 113 and 152 hours based on baseline-unadjusted concentrations. Group mean oral clearance and volume of distribution of total EPA in plasma ranged between 0.776 and 0.684 L/hr and between 80 and 88 L, respectively, based on baseline-adjusted concentrations. Accumulation of EPA was observed with BID dosing, with quantifiable trough concentrations of total and unesterified EPA in plasma. Steady state was approximately reached by Day 14 (Figure 12). Dose-normalized exposures of 2 g/day or 4 g/day ethyl-EPA were comparable, indicating approximately linear PK in this dose range.

In general, exposures of total EPA in plasma were higher than exposures in RBCs. After 28 days of dosing with ethyl-EPA, maximum EPA concentrations occurred later in RBCs compared with plasma (T_{max} = 8 to 12 hr). Accumulation of EPA in RBCs was observed with BID dosing.

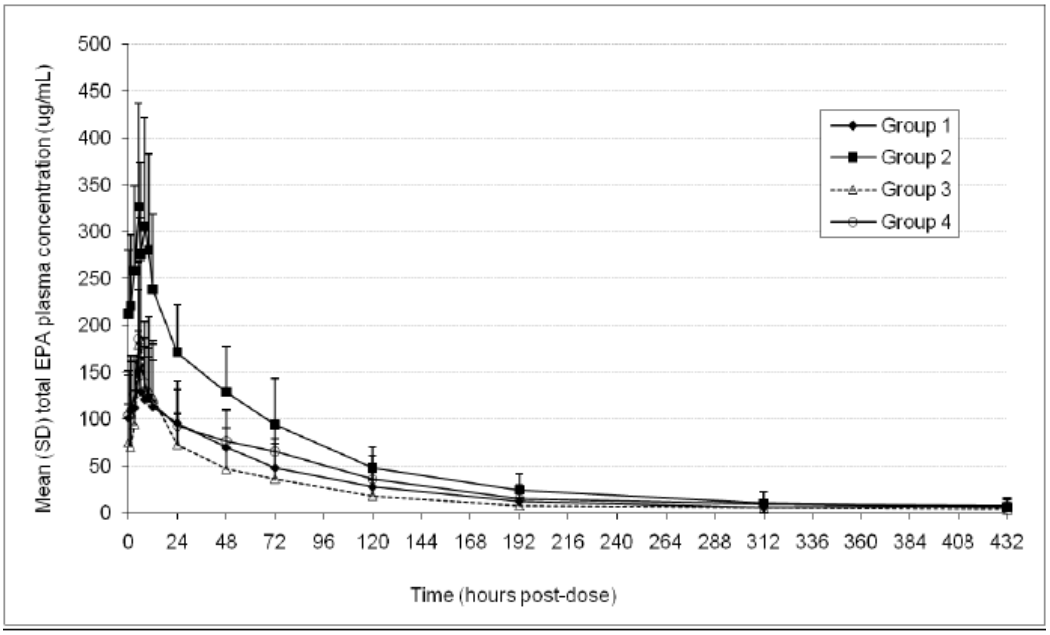
Trough concentrations showed that the RBC concentrations slowly increased over the duration of treatment and that steady state was not reached by Day 28.

Table 10 Pharmacokinetic Parameters of EPA after 28 days of 2 or 4 g/day Ethyl-EPA (Treatment Groups 1 and 2)

Mean (SD) or Median (IQR)[1]	Vascepa Dose in g/day	EPA Baseline (µg/mL)	C_{max} (µg/mL)	T_{max} (hr)	C_{min} (µg/mL)	AUC_{0-24hr} (µg*hr/mL)	$T_{1/2}$ (hr)	V_z/F (L)	CL/F (mL/hr)	C_{max} Ratio (CI)	AUC_{0-24hr} Ratio (CI)
Baseline-adjusted											
Total Plasma EPA	2 (Group1)	7.9 (7.0)	155 (49)	5 (0)	101 (50)	2907 (1160)	75 (46)	80 (63)	776 (257)	0.86 (63,116)	0.83 (62,109)
	4 (Group 2)	19.3 (16.1)	347 (113)	5 (0)	212 (68)	6519 (1963)	89 (42)	88 (55)	684 (281)		
Unesterified Plasma EPA	2 (Group1)	0.13 (0.12)	0.66 (0.34)	5 (1)	0.41 (0.28)	6.94 (3.07)	81 (38)	3.32^2 (0.81)	3.64^3 (2.14)	0.94 (70, 127)	0.69 (49, 96)
	4 (Group 2)	0.078 (0.047)	1.44 (0.41)	5 (2)	1.06 (0.56)	18.4 (4.58)	97 (37)	2.82^2 (1.09)	2.34^3 (0.81)		
RBC EPA	2 (Group1)	5.68 (4.31)	42 (14)	12 (14)	31 (12)	802 (268)	NC	NC	NC	1.05 (81, 137)	1.03 (71, 149)
	4 (Group 2)	12.1 (15.7)	77 (25)	8 (4)	64 (22)	1472 (450)	NC	NC	NC		
Baseline-unadjusted											
Total Plasma EPA	2 (Group1)	7.9 (7.0)	163 (53)	5 (0)	109 (53)	3098 (1233)	113 (53)	105 (55)	730 (248)	0.85 (63, 116)	0.82 (63, 107)
	4 (Group 2)	19.3 (16.1)	366 (116)	5 (0)	231 (69)	6983 (2009)	152 (53)	155 (132)	630 (241)		
Unesterified Plasma EPA	2 (Group1)	0.13 (0.12)	0.77 (0.29)	5 (1)	0.51 (0.27)	8.79 (2.57)	213 (NC)	6.24^2 (NC)	2.50^3 (0.86)	0.95 (72, 126)	0.84 (68, 104)
	4 (Group 2)	0.078 (0.047)	1.52 (0.41)	5 (2)	1.14 (0.58)	20.3 (4.71)	146 (9.4)	3.54^2 (0.48)	2.10^3 (0.65)		
RBC EPA	2 (Group1)	5.68 (4.31)	48 (14)	12 (14)	37 (15)	938 (328)	NC	NC	NC	1.01 (80, 128)	0.97 (72, 131)
	4 (Group 2)	12.1 (15.7)	89 (22)	8 (4)	76 (20)	1760 (405)	NC	NC	NC		

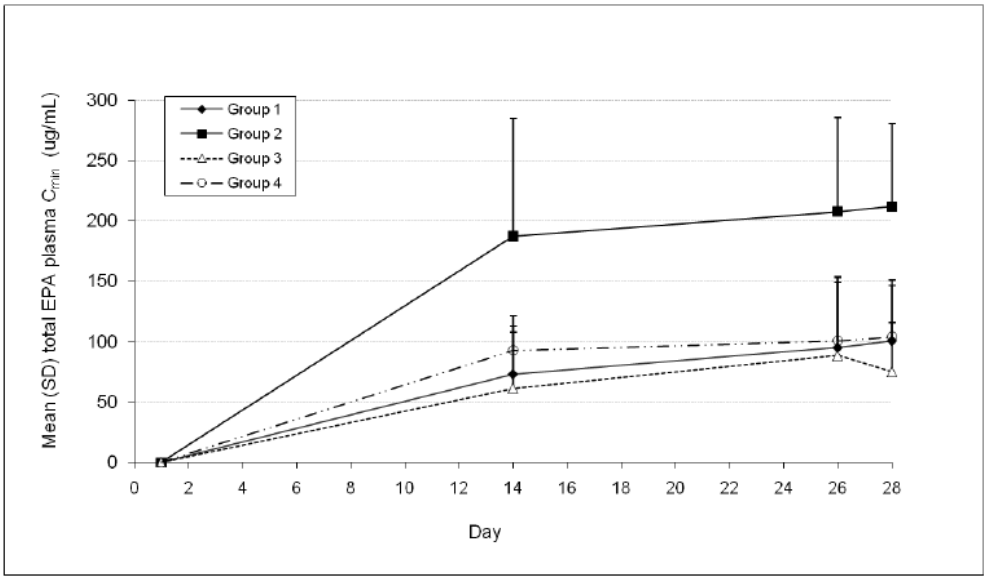
Group 1: 2 g/day Vascepa: one 1 g Vascepa capsule in the morning and one 1 g Vascepa capsule in the evening.
Group 2: 4 g/day Vascepa: two 1 g Vascepa capsules in the morning and two 1 g Vascepa capsules in the evening.
Data from Treatment Groups 1 (N=10) and 2 (N=9)
[1]Median and interquartile range (IQR) for T_{max}; mean and standard deviation (SD) for all other PK parameters, except ratios which show mean and 90% confidence intervals (CI).
[2] mean and SD × 10^4
[3] mean and SD × 10^5
NC = Could not be calculated or not reported because the number of reportable values was too small. RBC = red blood cell.
Ratios of C_{max} and AUC_{0-24hr} refer to dose-normalized ratios of Group 1 / Group 2.
Source: Study AMR-01-01-0018 CSR

Figure 11 Mean (SD) Baseline-Adjusted Total EPA Plasma Concentration versus Time on Day 28 from Time 0 to 432 h Post-Dose by Treatment



Group 1: 2 g/day Vascepa: one 1 g Vascepa capsule in the morning and one 1 g Vascepa capsule in the evening.
Group 2: 4 g/day Vascepa: two 1 g Vascepa capsules in the morning and two 1 g Vascepa capsules in the evening.
Group 3: 2 g/day Vascepa: two 1 g Vascepa capsules in the morning.
Group 4: 2 g/day Vascepa: two 0.5 g Vascepa capsules in the morning and two 0.5 g Vascepa capsules in the evening.
Source: Study AMR-01-01-0018 CSR

Figure 12 Mean (SD) Baseline-Adjusted Total EPA Plasma Trough Concentration (C_{min}) versus Time by Treatment



Group 1: AMR101 2 g daily: one AMR101 1000 mg capsule in the morning and one AMR101 1000 mg capsule in the evening.
Group 2: AMR101 4 g daily: two AMR101 1000 mg capsules in the morning and two AMR101 1000 mg capsules in the evening.
Group 3: AMR101 2 g daily: two AMR101 1000 mg capsules in the morning.
Group 4: AMR101 2 g daily: two AMR101 500 mg capsules in the morning and two AMR101 500 mg capsules in the evening.

(b) (4) PK comparison between BID and QD dosing regimen of

2 g/day dose was not evaluated.

The sponsor compared ethyl-EPA PK at 1 g BID for the two strengths, 0.5 g and 1 g. No changes were made in the ethyl-EPA formulation during the development program. Only the capsule strength was changed: initially, 0.5 g capsules were used in the clinical studies (CNS program); later, 1 g capsules were used (hypertriglyceridemia program). The [redacted] (b) (4) soft gelatin capsules is different between both strengths but the drug substance and all inactive ingredients are scaled proportionally between both formulations. The sponsor plans to market the 1 g ethyl-EPA capsules. The clinical studies conducted with the 0.5 g ethyl-EPA capsules (CNS studies) are used to support the safety profile of ethyl-EPA.

In general, the 0.5 g and 1 g ethyl-EPA capsules when administered at the same daily dose of 2 g/day resulted in similar AUCs, C_{max} and C_{min} (Table 11). Therefore, the 0.5 g and 1 g ethyl-EPA capsules can be considered comparable with regards to exposure.

Table 11 Pharmacokinetic Parameters of EPA after 28 days of 2 g/day Ethyl-EPA (Treatment Groups 1 and 2) with 1 g and 0.5 g Ethyl-EPA Capsules (Baseline-adjusted)

Mean (SD) or Median (IQR) [1]	Vascepa Capsule Strength	C_{max} µg/mL	T_{max} hr	C_{min} µg/mL	AUC_{0-24hr} µg*hr/mL
Total Plasma EPA	1 g (Group 1)	155 (49)	5 (0)	101 (50)	2907 (1160)
	0.5 g (Group 4)	211 (93)	6 (2)	104 (42)	3233 (1104)
Unesterified Plasma EPA	1 g (Group 1)	0.66 (0.34)	5 (1)	0.41 (0.28)	6.94 (3.07)
	0.5 g (Group 4)	0.70 (0.24)	(2)	0.44 (0.24)	7.51 (2.64)
RBC EPA	1 g (Group 1)	42 (14)	12 (14)	31 (12)	802 (268)
	0.5 g (Group 4)	38 (16)	24 (42)	26 (18)	574 (336)

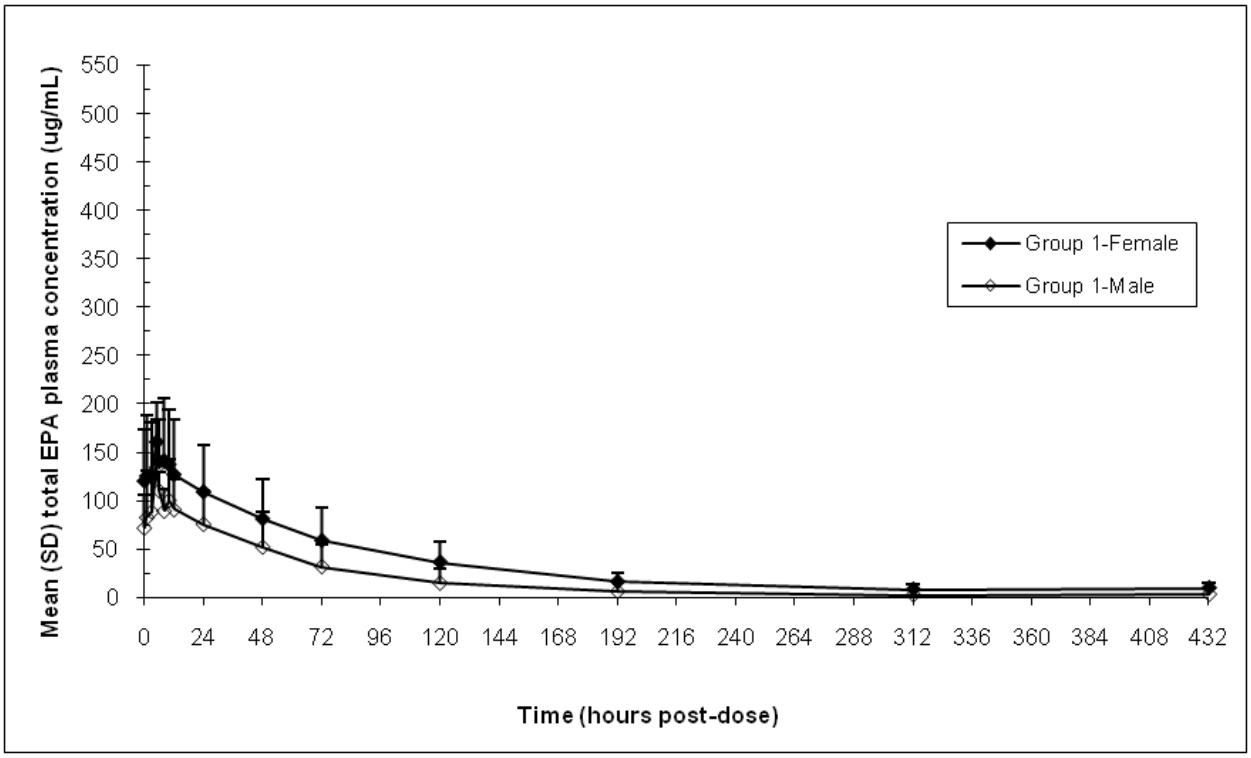
Group 1: 2 g/day Vascepa: one 1 g Vascepa capsule in the morning and one 1 g Vascepa capsule in the evening.
Group 4: 2 g/day Vascepa: two 0.5 g Vascepa capsules in the morning and two 0.5 g Vascepa capsules in the evening.
Data from Treatment Groups 1 (N=10) and 4 (N=12)
[1]Median and interquartile range (IQR) for T_{max}; mean and standard deviation (SD) for all other PK parameters.
Source: Study AMR-01-01-0018 CSR

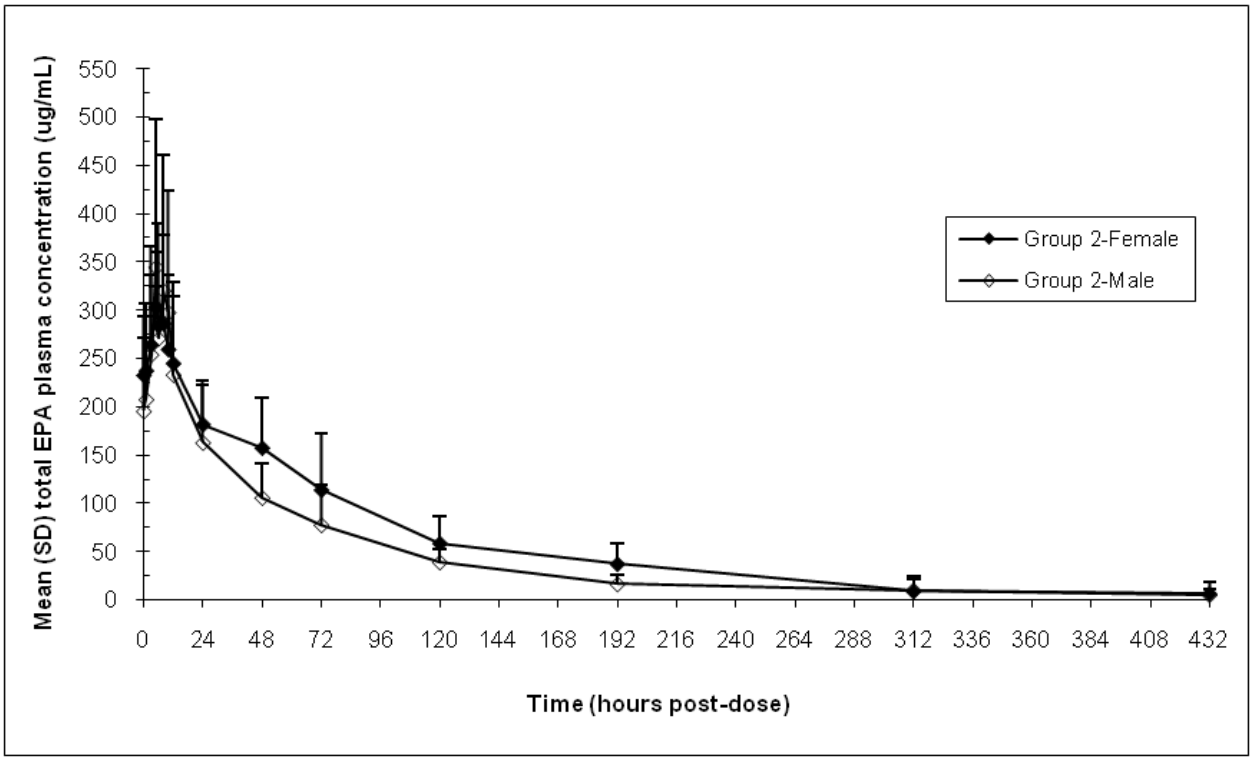
Effect of Gender on the PK

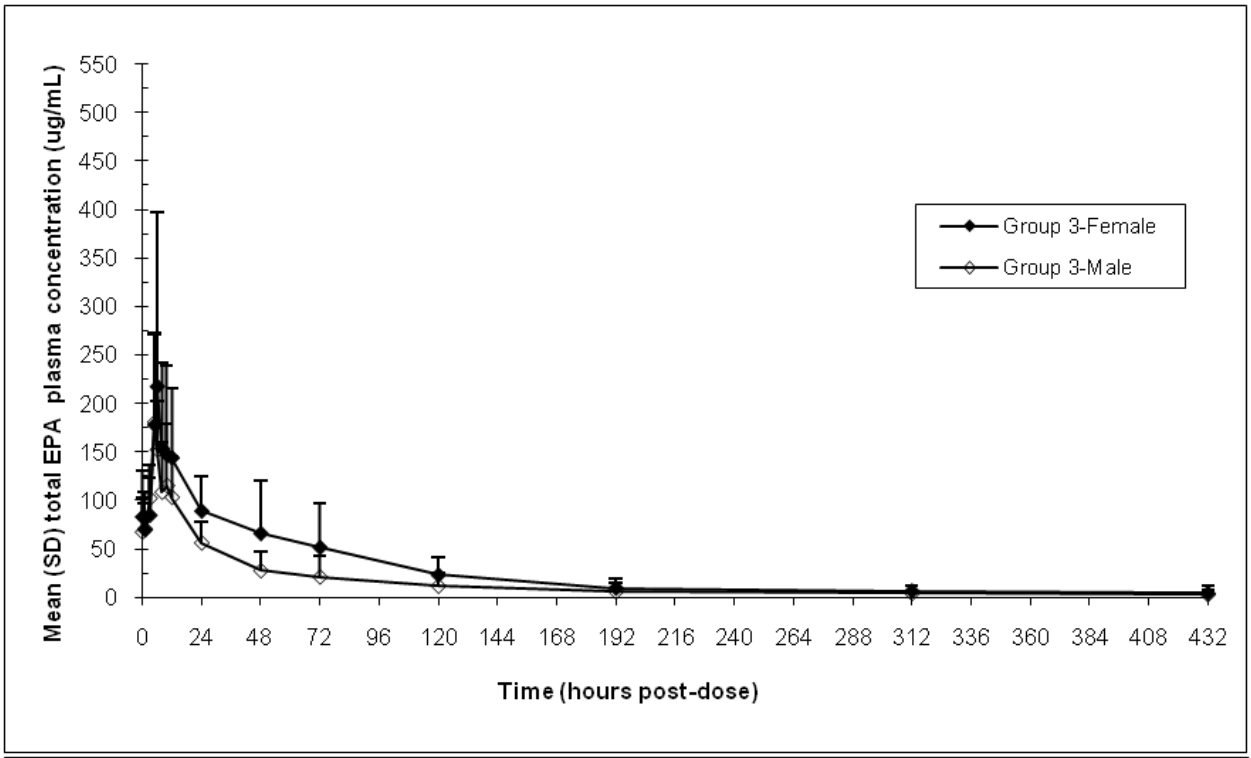
The effect of gender on EPA pharmacokinetics was examined graphically in Figure 13. There were 6, 4, 6 and 6 females in Treatment Groups 1, 2, 3 and 4, respectively, and 4, 5, 6 and 6 males in Treatment Groups 1, 2, 3 and 4 respectively.

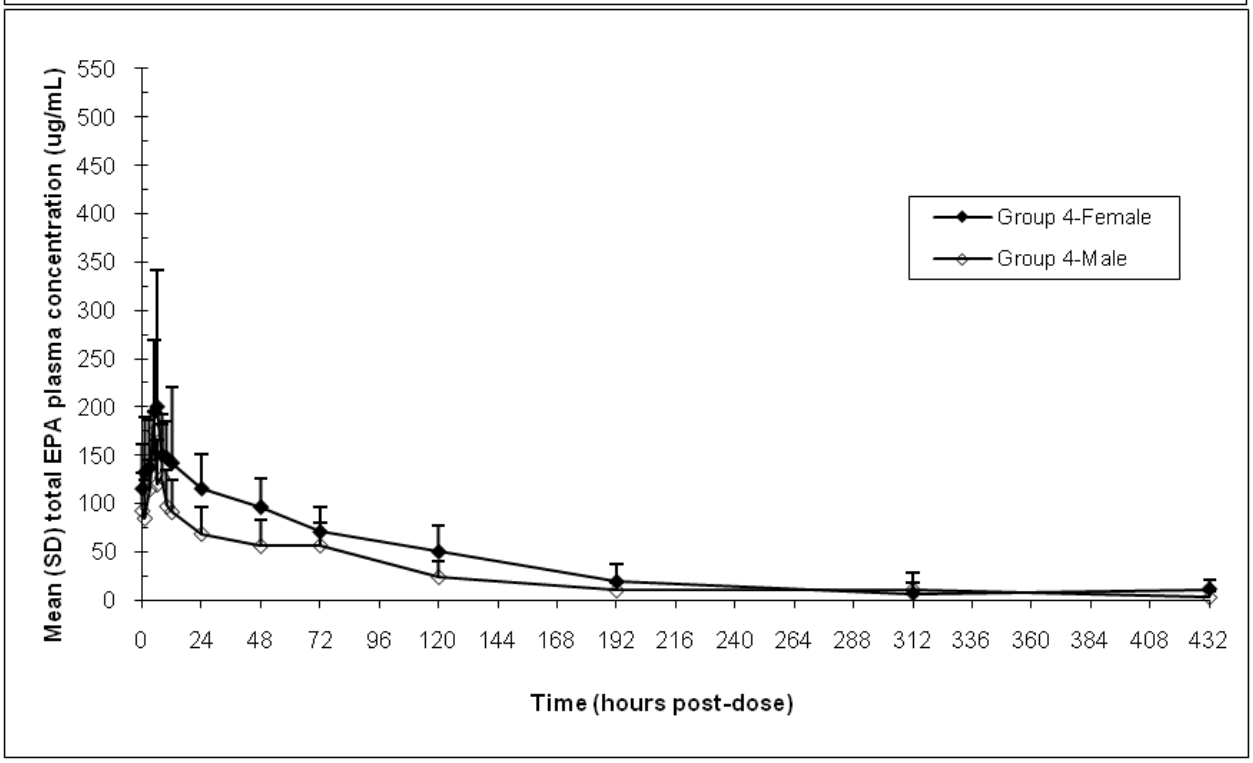
Mean EPA plasma concentration over time on Day 28 appeared similar among males and females, values appeared slightly lower for males compared to females. Figure 14 displays the relationship between EPA AUC_{0-24hr} and gender by treatment group, no significant gender effect was observed based on total exposure AUC_{0-24hr}.

Figure 13 Mean (SD) baseline-adjusted total EPA plasma concentration versus time on Day 28 from time 0 to 432 h by treatment and gender (linear scale) – Per protocol population



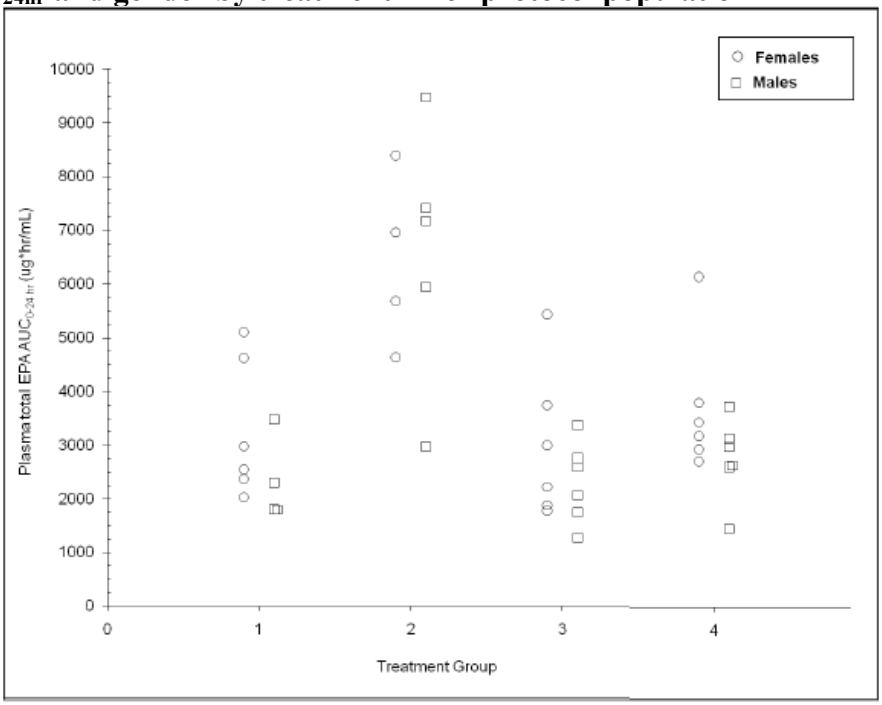






Group 1: AMR101 2 g daily: one AMR101 1000 mg capsule in the morning and one AMR101 1000 mg capsule in the evening.
Group 2: AMR101 4 g daily: two AMR101 1000 mg capsules in the morning and two AMR101 1000 mg capsules in the evening.
Group 3: AMR101 2 g daily: two AMR101 1000 mg capsules in the morning.
Group 4: AMR101 2 g daily: two AMR101 500 mg capsules in the morning and two AMR101 500 mg capsules in the evening.

Figure 14 Scatter plot of relationship between baseline-adjusted plasma total EPA AUC_{0-24hr} and gender by treatment – Per protocol population

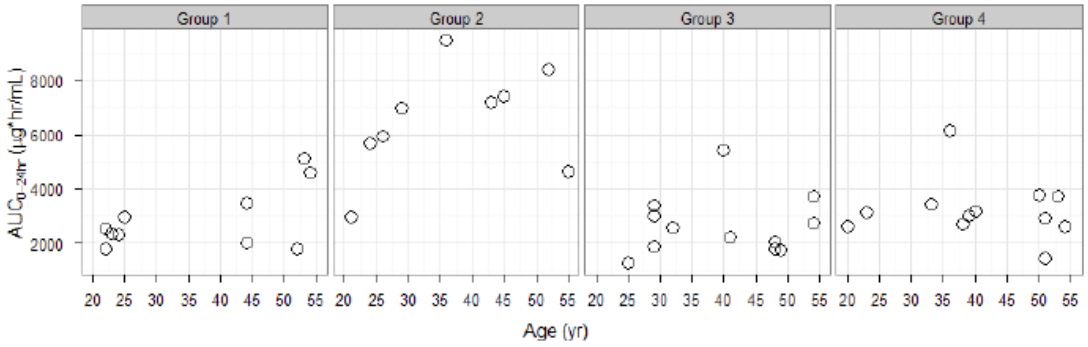


Group 1: AMR101 2 g daily: one AMR101 1000 mg capsule in the morning and one AMR101 1000 mg capsule in the evening.
Group 2: AMR101 4 g daily: two AMR101 1000 mg capsules in the morning and two AMR101 1000 mg capsules in the evening.
Group 3: AMR101 2 g daily: two AMR101 1000 mg capsules in the morning.
Group 4: AMR101 2 g daily: two AMR101 500 mg capsules in the morning and two AMR101 500 mg capsules in the evening.

Effect of Age on the PK

The effect of age on the EPA pharmacokinetics was examined graphically in Figure 15. No trends were observed between EPA exposure in plasma (AUC_{0-24hr}) and age (20-55 years) by treatment group.

Figure 15 Scatter plots of the relationship among AUC_{0-24hr} based on baseline adjusted total EPA concentrations in plasma, and age – Per protocol population



4.2.3 AMR-01-01-0020: Open-Label, Cross-Over, Drug-Drug Interaction Study between Ethyl-EPA and Omeprazole and between Ethyl-EPA and Rosiglitazone in Healthy Subjects

Objectives:

The objectives of this study were to determine whether ethyl-EPA 4 g/day at steady-state concentrations had an effect on the pharmacokinetics (PK) of omeprazole possibly through effects on CYP 2C19 and of rosiglitazone through effects on CYP 2C8.

Study design:

This was a Phase 1, single-center, open-label, cross-over, drug-drug interaction study between AMR101 and omeprazole and ethyl-EPA and rosiglitazone in healthy subjects. Thirty subjects were enrolled to receive:

• Omeprazole (40 mg/day, QD) on Days 1-7
• Rosiglitazone (8 mg) on Day 11
• AMR101 (4 g/day, BID) on Days 12-29
• Omeprazole (40 mg/day, QD) on Days 19-25
• Rosiglitazone (8 mg) on Day 29

Omeprazole was provided as 40 mg Prilosec® delayed-release capsules; rosiglitazone was provided as 8 mg Avandia® tablets, and AMR101 was provided as 1 g liquid-filled gelatin capsules.

Blood samples for the determination of omeprazole plasma concentrations were obtained prior to dosing on Day 1 and on Days 7 and 25 at time 0 (prior to dose) and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 14 and 24 hours after the omeprazole dose.

Blood samples for the determination of rosiglitazone plasma concentrations were obtained on Days 11 and 29 at time 0 (prior to dose) and 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, 12, 16 and 24 hours after the rosiglitazone dose.

Blood samples for the determination of unesterified and total EPA concentrations in plasma were obtained prior to the morning dose of AMR101 on Days 12, 25 and 29, and 5 hours following the AMR101 dose on Days 25 and 29.

Pharmacokinetic Endpoints:

• Omeprazole: Omeprazole PK (primary endpoint was $AUC_{0\text{-}24hr}$; secondary endpoints: C_{max} and T_{max}) were determined based on omeprazole plasma concentrations on Days 7 and 25 (without and with AMR101).

• Rosiglitazone: Rosiglitazone PK (primary endpoint was $AUC_{0\text{-}inf}$; secondary endpoints: C_{max}, $AUC_{0\text{-}24hr}$, and T_{max}) were determined based on rosiglitazone plasma concentrations on Days 11 and 29 (without and with AMR101).

Pharmacokinetic Analyses:

Descriptive statistics were calculated for omeprazole and rosiglitazone concentrations in plasma, and for unesterified and total EPA concentrations in plasma. Comparisons for omeprazole and rosiglitazone were made only where measurements without and with AMR101 were available. When both measurements were not available (e.g., early termination), data was listed, but not included in the comparisons.

Omeprazole and rosiglitazone PK parameters: PK parameters (C_{max}, T_{max}, $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}inf}$, and $T_{1/2}$) were computed for each subject per day (without and with AMR101) with non-compartmental methods using the actual sampling times. Descriptive statistics were calculated for the PK parameters per day (without and with AMR101). The effect of AMR101 on the exposure of omeprazole and rosiglitazone was determined by a PK comparison between the exposure of omeprazole and rosiglitazone administered alone versus each drug administered with AMR101. The primary PK comparisons were based on the $AUC_{0\text{-}24hr}$ of omeprazole and on the $AUC_{0\text{-}inf}$ of rosiglitazone. Analysis of variance (ANOVA) models under the cross-over design were used for analyzing all AUC and C_{max} parameters, and based on natural logtransformed values. This included the effects for treatment (without and with AMR101) as a random effect. The estimate of the ratio between two treatments for these parameters and the corresponding 90% confidence intervals (CI) for the ratio were obtained by exponentiating the difference in logarithms, and used for assessing PK of the two treatments (without and with AMR101) within each PK comparison. For T_{max} and $T_{1/2}$ of omeprazole and rosiglitazone, summary statistics are provided.

Study results:

A total of 30 healthy subjects (19 male, 11 female) were enrolled in the study and 28 (93.3%) subjects completed the study as planned. Two subjects discontinued prematurely due to study noncompliance. Mean (SD) omeprazole and rosiglitazone plasma concentration without and with AMR101 versus time are displayed on linear scales in Figure 16 and Figure 17, respectively. The PK parameters of omeprazole and rosiglitazone and their respective comparisons with and without ethyl-EPA are listed in Table 12.

Figure 16 Mean (SD) Omeprazole Plasma Concentration without and with AMR101 versus Time

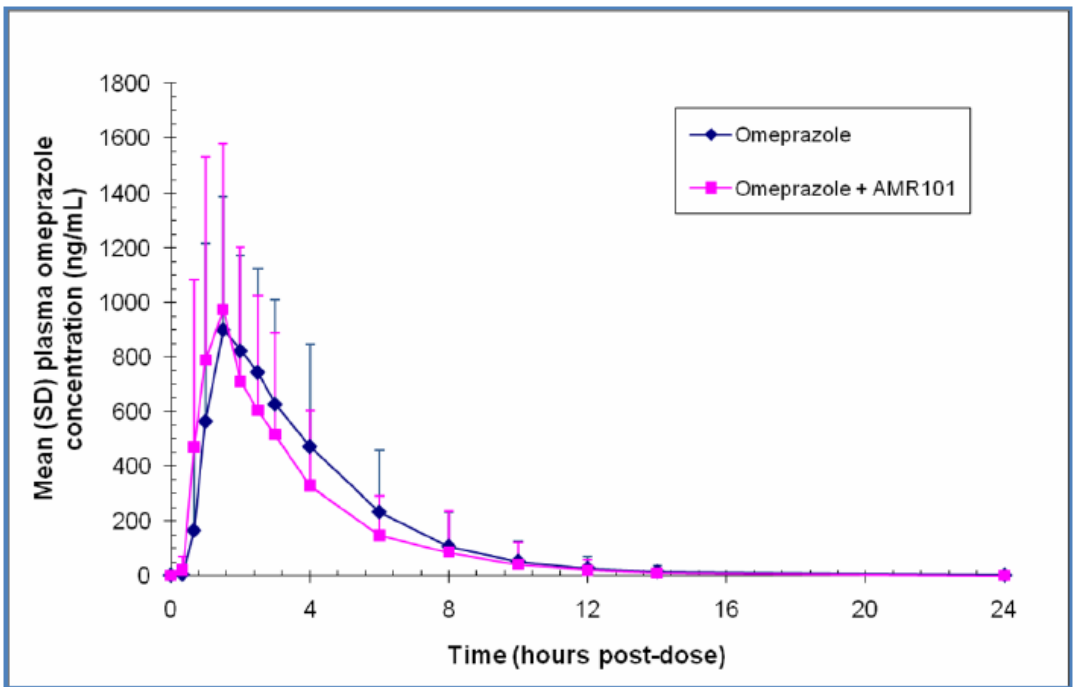


Figure 17 Mean (SD) Rosiglitazone Plasma Concentration without and with AMR101 versus Time

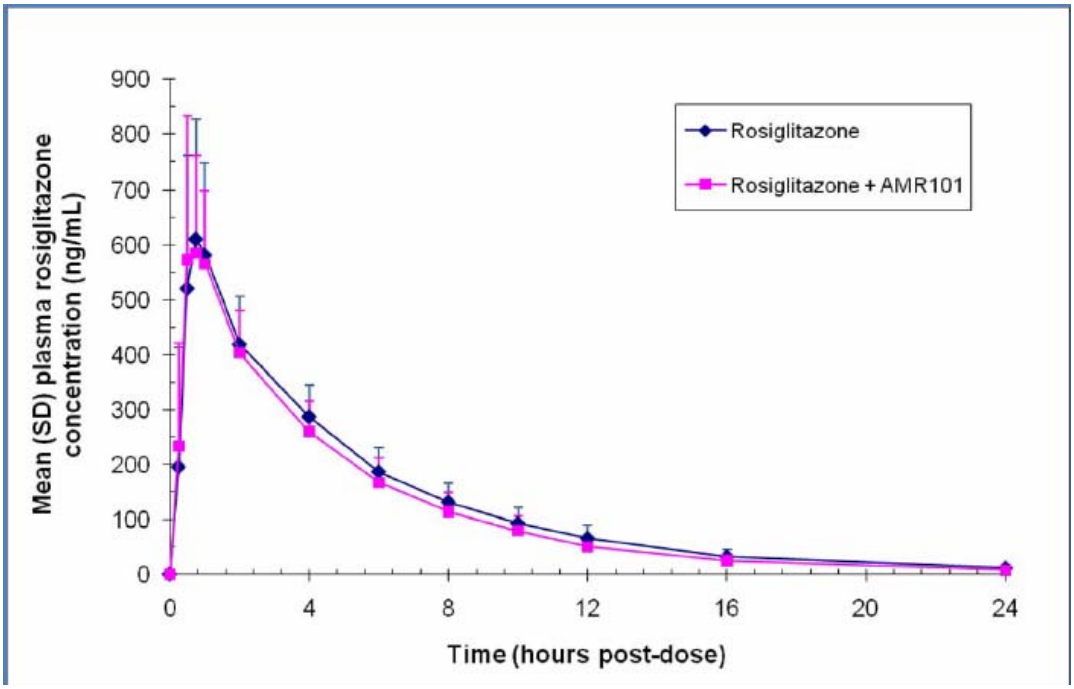


Table 12 Pharmacokinetic Parameters of Omeprazole and Rosiglitazone in the Presence and Absence of Ethyl-EPA

Analyte	Vascepa	C_{max} (ng/mL)	AUC* (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} Ratio (90% CI)	AUC* Ratio (90% CI)
omeprazole	No	1156 (461)	3607 (2208)	NA	1.5 (1.0, 6.0)	1.5 (0.7)	1.01 (87.4, 116.3)	0.84 (76.0, 91.9)
	Yes	1222 (621)	3142 (2114)	NA	1.5 (0.7, 8.0)	1.4 (0.7)		
rosiglitazone	No	672 (185)	3152 (648)	3228 (679)	0.8 (0.5, 2.0)	4.4 (0.7)	1.01 (92.0, 109.9)	0.90 (87.0, 93.4)
	Yes	673 (170)	2873 (654)	2921 (677)	0.8 (0.5, 2.0)	4.1 (0.7)		

Mean (SD) displayed for all PK parameters except T_{max} displayed as median (min, max).
Ratios are geometric mean ratios of treatment with Vascepa / treatment without Vascepa.
* AUC refers to AUC_{τ} for omeprazole where τ = 24 hr, and refers to $AUC_{0-\infty}$ for rosiglitazone
CI = confidence interval in percent
Source: Study AMR-01-01-0020 CSR

The ratio of the geometric means of C_{max} following administration of omeprazole with and without ethyl-EPA was 1.01 and the 90% confidence limits were 87.4% and 116.3%. The ratio of the geometric means of AUC_{0-24hr} following administration of omeprazole with ethyl-EPA versus without ethyl-EPA was 0.84 and the 90% confidence limits were 76.0% and 91.9%. It is concluded that 4 g/day ethyl-EPA does not inhibit the metabolism of omeprazole.

The ratio of the geometric means of C_{max} following administration of rosiglitazone with and without ethyl-EPA was 1.01 and the 90% confidence limits were 92.0% and 109.9%. The ratio of the geometric means of $AUC_{0-\infty}$ following administration of rosiglitazone with and without ethyl-EPA was 0.90 and the 90% confidence limits were 87.0% and 93.4%. It is concluded that 4 g/day ethyl-EPA does not inhibit the metabolism of rosiglitazone.

4.2.4 AMR-01-01-0021: A Phase 1, Open-Label, Crossover Study to Evaluate the Effect of Icosapent Ethyl (AMR101) on the Single-Dose Pharmacokinetics and Anticoagulation Pharmacodynamics of Warfarin in Healthy Subjects

Objectives:

The objectives of this study were to investigate the effect of AMR101 on the pharmacokinetics (PK) and anticoagulation pharmacodynamics (PD) (prothrombin time [PT] and International Normalized Ratio [INR]) of warfarin in healthy subjects.

Study design:

This was a Phase 1, single-center, open-label, cross-over, drug-drug interaction study between AMR101 and warfarin in healthy subjects. Twenty-six subjects were enrolled to receive:

- Warfarin (25 mg) on Day 1
- AMR101 (4 g/day, BID) on Days 8-35
- Warfarin (25 mg) on Day 29

Warfarin was provided as Coumadin® tablets (two 10 mg and one 5 mg tablets). AMR101 was provided as 1 g liquid-filled gelatin capsules. Warfarin was administered approximately 30 minutes before breakfast, while ethyl-EPA was administered with food.

Blood samples for the determination of R- and S-warfarin plasma concentrations were obtained on Days 1 and 29 at time 0 (prior to dose) and 0.5, 1, 1.5, 2, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144 and 168 hours after the warfarin dose.

Blood samples for the determination of unesterified and total EPA plasma concentrations were obtained prior to the morning dose of AMR101 on Days 8, 29 and 35, and 5 hours following the morning AMR101 dose on Days 29 and 35.

Blood samples for assessment of PT and INR were obtained at screening and on Days 1 and 29 at time 0 (prior to dose) and 6, 12, 24, 36, 48, 72, 96, 120, 144 and 168 hours after the warfarin dose.

Pharmacokinetic Endpoints:

• Warfarin: $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, $T_{1/2}$ and λz of the R- and S-enantiomers of warfarin when warfarin was administered alone compared to when warfarin was administered with AMR101.

• EPA: Total and unesterified EPA plasma concentrations and the ratio of unesterified EPA to total EPA plasma concentrations on Days 8, 29 and 35 (descriptive statistics only of the concentrations per day and time).

Pharmacodynamic Endpoints:

• Maximum anticoagulant effect (INR_{max}), the time of maximum anticoagulation (T_{INRmax}) and the area under the INR effect versus time curve (AUC_{INR}) when warfarin was administered alone compared to when warfarin was administered with AMR101.

Pharmacokinetic Analyses:

The effect of AMR101 on the exposure of R- and S-warfarin was determined by a PK comparison between R- and S-warfarin when warfarin was administered alone versus when warfarin administered with AMR101. The primary PK comparison was based on the $AUC_{0\text{-inf}}$ and C_{max} of R- and S-warfarin.

Analysis of variance (ANOVA) models under the cross-over design were used for analyzing all AUC and C_{max} parameters, and were based on natural log-transformed values. This included treatment (without and with AMR101) as a fixed effect, and subject as a random effect. The estimate of the ratio between two treatments for these parameters and the corresponding 90% confidence intervals (CIs) for the ratio were obtained by exponentiating the difference in logarithms, and used for assessing similarity between warfarin (without and with AMR101) within each PK comparison. The treatment of warfarin alone administered on Day 1 was the reference treatment for the purpose of statistical comparisons.

A secondary comparison included T_{max} of R-warfarin and S-warfarin, analyzed without logtransformation using nonparametric Wilcoxon Signed Rank Test. The corresponding 95% CIs for the difference in medians was reported using Walsh Average and appropriate quantile of the

Wilcoxon Signed Rank Test Statistic. Significant difference for the treatment comparison was concluded if the resulting p value was <0.05.

Pharmacodynamic Analyses:

PD parameters (INR_{max}, T_{INRmax} and AUC_{INR}) were computed for each subject per day (without and with AMR101) with non-compartmental methods using the actual sampling times.

The effect of AMR101 on the anticoagulation PD effect of warfarin was determined by a comparison between the PD effects of warfarin when administered without versus with AMR101. The primary comparison for PD similarity was based on the INR_{max} and AUC_{INR}. Mixed effects ANOVA modeling under the cross-over design were used for analyzing these parameters based on natural log-transformed values. This model included treatment (without and with AMR101) as a fixed effect and subject as a random effect. The estimate of the ratio between two treatments for these parameters and the corresponding 90% CIs for the ratios were obtained by exponentiating the mean difference in logarithms. Significant differences for the treatment comparison were concluded if the resulting p value was <0.05.

Study results:

Warfarin consists of a pair of enantiomers that are metabolized differentially by CYPs. R-warfarin is metabolized primarily by CYP1A2 to 6- and 8-hydroxywarfarin, by CYP3A4 to 10-hydroxywarfarin, and by carbonyl reductases to diastereoisomeric alcohols. S-warfarin is metabolized primarily by CYP2C9 to 7-hydroxywarfarin. Mean (SD) R- and S-warfarin plasma concentrations without and with AMR101 versus time are plotted on a linear scale in Figure 18 and Figure 19, respectively. The PK parameters of warfarin and their comparisons with and without ethyl-EPA are listed in Table 13. The ratio of the geometric means of C_{max} following administration of warfarin with and without ethyl-EPA was 1.08 for R-warfarin and 1.11 for S-warfarin. The ratio of the geometric means of $AUC_{0-\infty}$ following administration of warfarin with ethyl-EPA versus without ethyl-EPA was 0.99 for R-warfarin and 1.00 for S-warfarin. The 90% confidence intervals were all between 80% and 125%. It is concluded that 4 g/day ethyl-EPA does not inhibit the metabolism of warfarin.

The PD parameters of the anticoagulation parameters of warfarin and their comparisons with and without ethyl-EPA are listed in Table 14. The ratio of the geometric means of INR_{max} following administration of warfarin with and without ethyl-EPA was 0.87, while the same ratio for AUC_{INR} was 0.94. The 90% confidence intervals were all between 80% and 125%. It is concluded that 4 g/day Vascepa does not affect the anticoagulation parameters of warfarin.

Figure 18 Mean (SD) R-warfarin Plasma Concentration without and with AMR101 versus Time

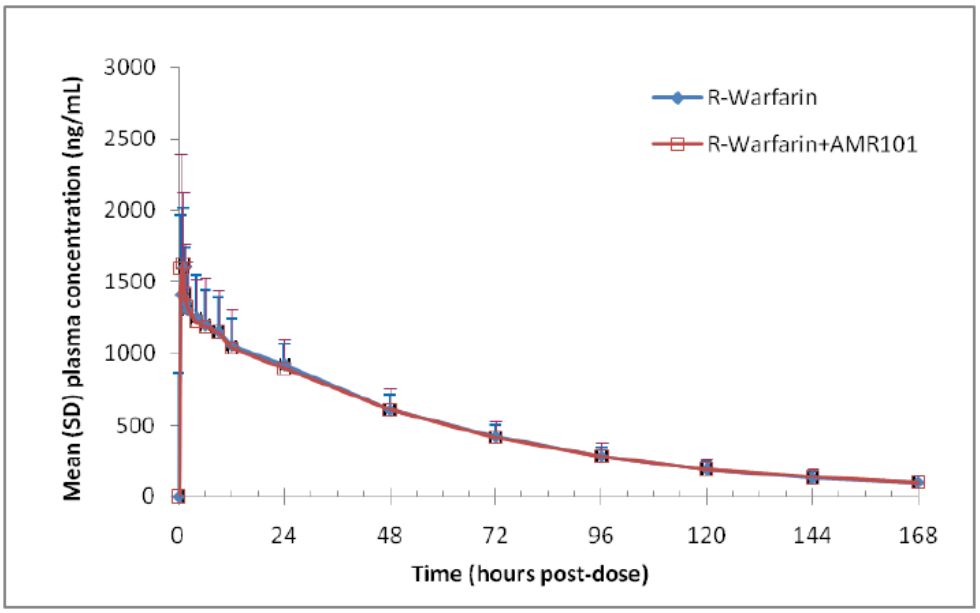


Figure 19 Mean (SD) S-warfarin Plasma Concentration without and with AMR101 versus Time

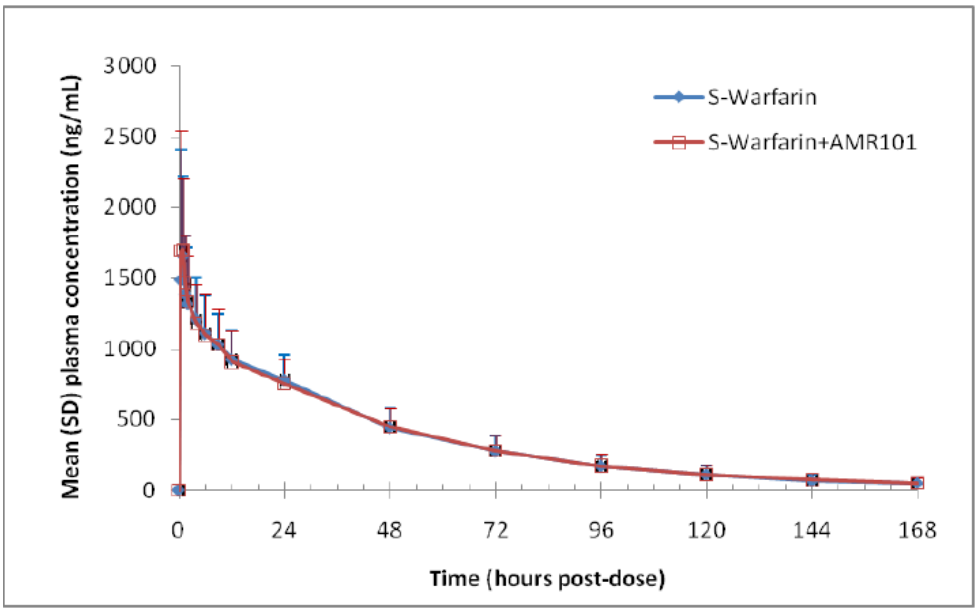


Table 13 Pharmacokinetic Parameters of Warfarin in the Presence and Absence of Ethyl-EPA

Analyte	Vascepa	C_{max} (µg/mL)	$AUC_{0-\infty}$ (µg*hr/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	C_{max} Ratio (90% CI)	$AUC_{0-\infty}$ Ratio (90% CI)
R-warfarin	No	1.77 (0.67)	82.6 (19.7)	1.0 (0.5, 9.0)	46.4 (8.4)	1.08 (99.1, 117.4)	0.99 (95.7, 102.9)
	Yes	1.87 (0.59)	82.5 (22.8)	1.0 (0.5, 1.5)	46.8 (8.3)		
S-warfarin	No	1.84 (0.73)	60.2 (15.0)	1.0 (0.5, 9.0)	36.7 (8.2)	1.11 (101.3, 120.6)	1.00 (96.5, 103.2)
	Yes	1.97 (0.62)	60.3 (16.2)	1.0 (0.5, 1.5)	37.7 (9.1)		

Mean (SD) displayed for all PK parameters except T_{max} displayed as median (min, max).
Ratios are geometric mean ratios of treatment with Vascepa / treatment without Vascepa.
CI = confidence interval in percent.
Source: Study AMR-01-01-0021 CSR

Table 14 Pharmacodynamic Parameters of Warfarin Anticoagulation in the Presence and Absence of Ethyl-EPA

Analyte	Vascepa	INR_{max}	AUC_{INR}	t_{INRmax} (hr)	INR_{max} Ratio (90% CI)	AUC_{INR} Ratio (90% CI)
Quantitation of anticoagulation due to warfarin	No	1.9 (0.5)	218 (28)	48 (24, 96)	0.87 (83.7, 89.5)	0.94 (92.6, 95.7)
	Yes	1.6 (0.4)	205 (25)	36 (24, 48)		

Mean (SD) displayed for all PD parameters except t_{INRmax} displayed as median (min, max).
Ratios are geometric mean ratios of treatment with Vascepa / treatment without Vascepa.
CI = confidence interval in percent
Source: Study AMR-01-01-0021 CSR

4.2.5 AMR-01-01-0023: A Phase 1, Open-Label, Crossover Drug-Drug Interaction Study to Evaluate the Effect of Icosapent Ethyl (AMR101) on the Pharmacokinetics of Atorvastatin in Healthy Subjects

Objectives:

The objective of this study was to investigate the effect of AMR101 on the pharmacokinetics (PK) of atorvastatin in healthy subjects.

Study design:

This was a Phase 1, single-center, open-label, cross-over, drug-drug interaction study between AMR101 and atorvastatin in healthy subjects. Thirty subjects were enrolled to receive:

- Atorvastatin (80 mg/day) once per day (QD) on Days 1-7
- AMR101 (4 g/day, twice per day (BID)) on Days 8-35
- Atorvastatin (80 mg/day) QD on Days 29-35

Atorvastatin was provided as Lipitor® tablets (80 mg). AMR101 was provided as 1 g liquid-filled gelatin capsules. Atorvastatin was administered approximately 1 hour before breakfast, while ethyl-EPA was administered with food.

Blood samples for the determination of atorvastatin and metabolites 2-hydroxyatorvastatin and 4-hydroxyatorvastatin plasma concentrations were obtained on Days 1 and 29 at time 0 (prior to dose) and on Days 7 and 35 at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after the atorvastatin dose.

Blood samples for the determination of unesterified and total EPA plasma concentrations were obtained prior to the morning dose of AMR101 on Days 8, 29 and 35, and 5 hours following the morning AMR101 dose on Days 29 and 35.

Pharmacokinetic Endpoints:

• Atorvastatin (and metabolites): AUC_{0-24}, C_{max} and T_{max} of atorvastatin (and metabolites) when administered alone compared to when administered with AMR101.
• EPA: Total and unesterified EPA plasma concentration on Days 8, 29 and 35 (descriptive statistics only of the concentrations per day and time).

Pharmacokinetic Analyses:

Atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin PK parameters AUC_{0-24hr}, C_{max} and T_{max} were computed for each subject per day (without and with AMR101) with non-compartmental methods using the actual sampling times. Descriptive statistics were calculated for the PK parameters per day (without and with AMR101).

The effect of AMR101 on the exposure of atorvastatin was determined by a PK comparison between atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin when atorvastatin was administered alone versus atorvastatin administered with AMR101. The primary PK comparison was based on the AUC_{0-24hr} and C_{max} of atorvastatin. Analysis of variance (ANOVA) models under the cross-over design were used for analyzing all AUC and C_{max} parameters, and based on natural log-transformed values. This included the effects for treatment (without and with AMR101) as a random effect. The estimate of the ratio between two treatments for these parameters and the corresponding 90% confidence intervals (CIs) for the ratio were obtained by exponentiating the difference in logarithms, and used for assessing similarity between atorvastatin (without and with AMR101) within each PK comparison. The treatment of atorvastatin alone was the reference treatment for the purpose of statistical comparisons.

Secondary comparisons included comparisons between treatments for AUC_{0-24hr} and C_{max} of 2-hydroxyatorvastatin and 4-hydroxyatorvastatin that were similar to the primary comparison; and nonparametric analysis of T_{max} of atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin using the Wilcoxon Signed Rank Test. The corresponding 95% CIs for the difference in medians was reported using Walsh Average and appropriate quantile of the Wilcoxon Signed Rank Test Statistic. Significant difference for the treatment comparison was concluded if the resulting p value was <0.05.

Study results:

Mean (SD) atorvastatin, 2-hydroxyatorvastatin and 4-hydroxyatorvastatin plasma concentrations

without and with AMR101 versus time are displayed on linear scales in Figure 20, Figure 21 and Figure 22, respectively. The PK parameters of atorvastatin and its metabolites and their comparisons with and without ethyl-EPA are listed in Table 15. The ratios of the geometric means of C_{max} for atorvastatin and its 2-hydroxy and 4-hydroxy metabolites, following administration of atorvastatin with and without ethyl-EPA were 1.08, 1.04 and 0.97, respectively. The ratio of the geometric means of AUC_{τ} for atorvastatin and its 2-hydroxy and 4-hydroxy metabolites, following administration of atorvastatin with and without ethyl-EPA were 0.99, 0.91, and 0.92, respectively. The 90% confidence intervals for C_{max} and $AUC_{0-\infty}$ were between 80% and 125% for atorvastatin and its metabolites. It is concluded that 4 g/day ethyl-EPA does not inhibit the metabolism of atorvastatin.

Figure 20 Mean (SD) Atorvastatin Plasma Concentration without and with AMR101 versus Time

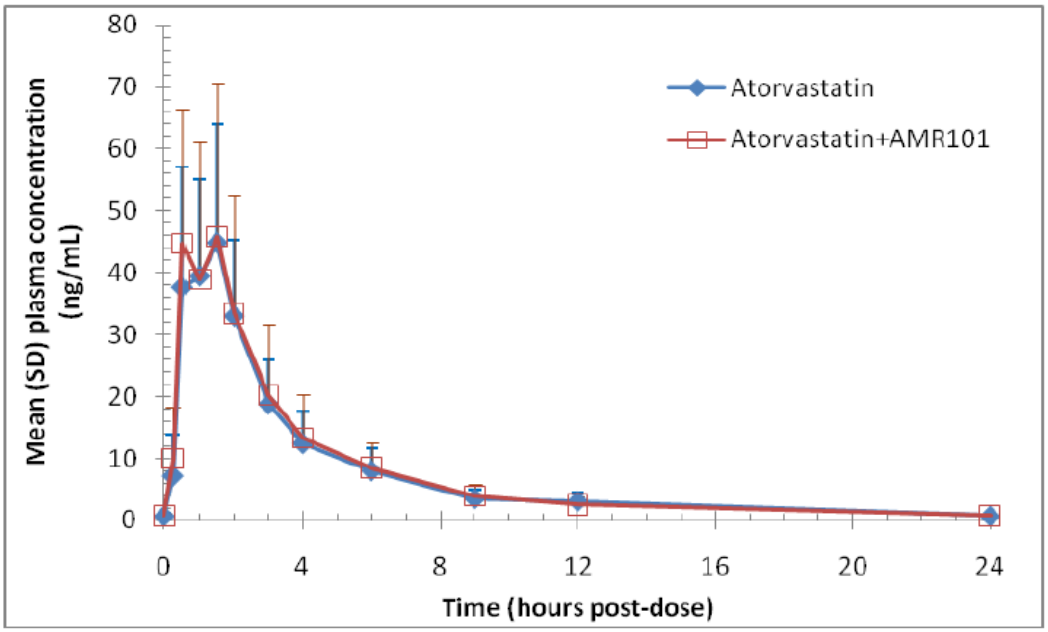


Figure 21 Mean (SD) 2-hydroxyatorvastatin plasma concentration without and with AMR101 versus time

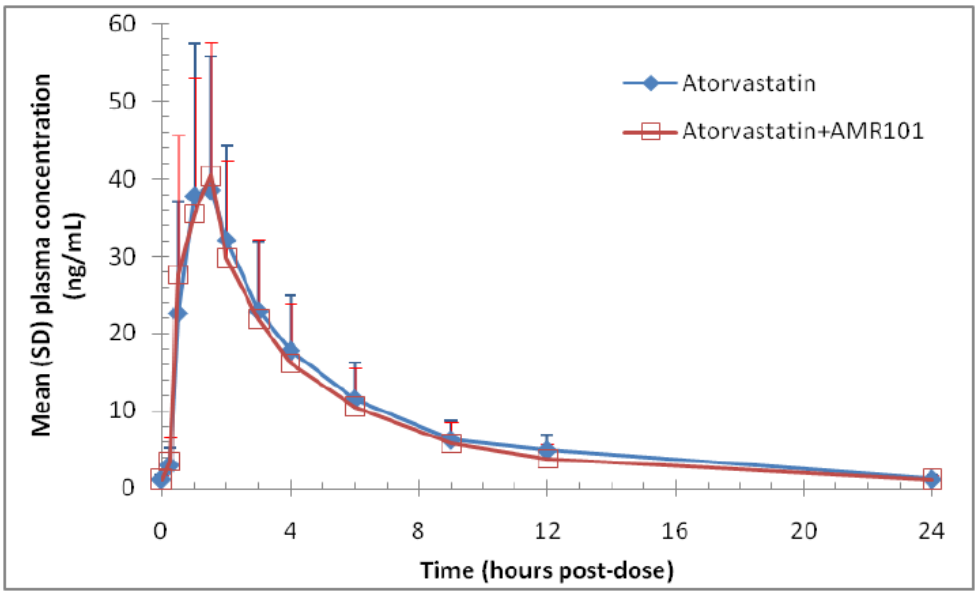


Figure 22 Mean (SD) 4-hydroxyatorvastatin plasma concentration without and with AMR101 versus time

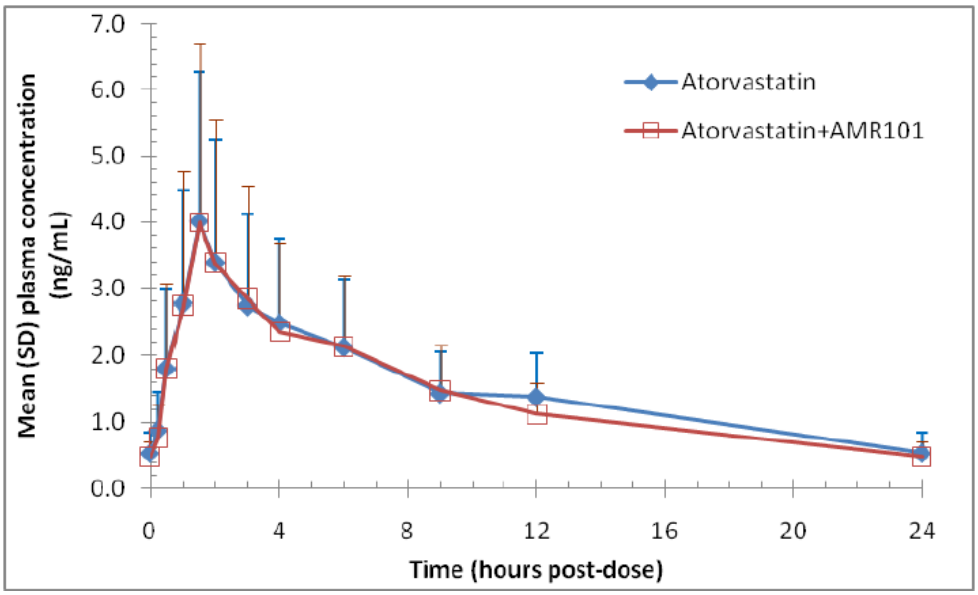


Table 15 Pharmacokinetic Parameters of Atorvastatin, 2-Hydroxy Atorvastatin, and 4-Hydroxy Atorvastatin in the Presence and Absence of Ethyl-EPA

Analyte	Vascepa	C_{max} (ng/mL)	AUC_{τ} (ng*hr/mL)	T_{max} (hr)	C_{max} Ratio (90% CI)	AUC_{τ} Ratio (90% CI)
atorvastatin	No	52.7 (19.3)	179.8 (59.5)	1.0 (0.5, 1.0)	1.08 (94.9, 122.1)	0.99 (90.2, 108.9)
	Yes	57.1 (21.9)	184.3 (79.3)	0.5 (0.5, 1.5)		
2-hydroxy atorvastatin	No	43.2 (18.8)	213.1 (73.0)	1.25 (0.5, 3.0)	1.04 (89.1, 121.3)	0.91 (82.8, 99.7)
	Yes	44.5 (17.4)	196.7 (77.0)	1.25 (0.5, 2.0)		
4-hydroxy atorvastatin	No	4.14 (2.21)	36.7 (16.4)	1.5 (1.0, 3.0)	0.97 (78.0, 117.3)	0.92 (82.3, 102.8)
	Yes	4.20 (2.66)	34.3 (16.4)	1.5 (1.5, 6.0)		

Mean (SD) displayed for all PK parameters except T_{max} displayed as median (min, max).
Ratios are geometric mean ratios of treatment with Vascepa / treatment without Vascepa.
τ = 24 hr; CI = confidence interval in percent
Source: Study AMR-01-01-0023 CSR

4.3 CLINICAL PHARMACOLOGY FILING MEMO

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	NDA 202057	Brand Name	Vascepa™
OCP Division (I, II, III, IV, V)	II	Generic Name	ethyl-EPA
Medical Division	DMEP	Drug Class	Omega-3 fatty acid
OCP Reviewer	Zhihong Li	Indication(s)	Severe hypertriglyceridemia
OCP Team Leader	Jayabharathi Vaidyanathan	Dosage Form	Soft gelatin capsule
Pharmacometrics Reviewer	TBD	Dosing Regimen	4 g/day as BID. (b) (4) (b) (4)
Date of Submission	9/26/2011	Route of Administration	Oral
Estimated Due Date of OCP Review	5/26/2012	Sponsor	Amarin Pharmaceuticals Ireland Ltd.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date	7/26/2012		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	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		Test Facility Study No. 310873, 311369, 313125
I. Clinical Pharmacology		9		LA01.01.0009, AMR-01-01-0018, AMR-01-01-0020, AMR-01-01-0021, AMR-01-01-0023, AMR-NC-11-01, OPT-2010-157, AMR-01-01-0016, AMR-01-01-0017
Mass balance:				
Isozyme characterization:	X	1		AMR-NC-11-01
Blood/plasma ratio:				
Plasma protein binding:	X	1		789867
Pharmacokinetics (e.g., Phase I) -	X	4		LA01.01.0009, AMR-01-01-0018, AMR-01-01-0016, AMR-01-01-0017
Healthy Volunteers-		2		LA01.01.0009, AMR-01-01-0018
single dose:	X	1		LA01.01.0009
multiple dose:	X	2		LA01.01.0009, AMR-01-01-0018
Patients-				
single dose:				
multiple dose:	X	2		AMR-01-01-0016, AMR-01-01-0017
Dose proportionality -	X	1		AMR-01-01-0018
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		AMR-01-01-0018
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects of primary drug:	X	3		AMR-01-01-0020, AMR-01-01-0021, AMR-01-01-0023
In-vitro:	X	2		AMR-NC-11-01, OPT-2010-157
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	X	2		AMR-01-01-0016, AMR-01-01-0017
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		AMR-01-01-0016, AMR-01-01-0017
Population Analyses -				
Data rich:				
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				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		12		LA01.01.0009, AMR-01-01-0018, AMR-01-01-0020, AMR-01-01-0021, AMR-01-01-0023, AMR-NC-11-01, OPT-2010-157, AMR-01-01-0016, AMR-01-01-0017, Test Facility Study No. 310873, 311369, 313125

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	No formulation change
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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	
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	
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.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

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

None.

Zhihong Li, Ph.D.	11/09/2011
Reviewing Clinical Pharmacologist	Date
Jayabharathi Vaidyanathan, Ph.D.	11/09/2011
Team Leader/Supervisor	Date

RECOMMENDATIONS:

- This NDA application is fileable from a clinical pharmacology perspective
- No comments in the 74-day letter
- No DSI inspection needed for Clinical Pharmacology studies

BACKGROUND:

In accordance with 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 USC §355) and 21 CFR §314.50, Amarin Pharmaceuticals Ireland Ltd. has submitted this original New Drug Application (NDA 202057) for Vascepa™ as an adjunct to diet to reduce triglyceride (b) (4) levels in patients with very high (≥500 mg/dL) triglycerides.

Vascepa™ (icosapent ethyl) is a highly purified formulation of ethyl eicosapentaenoic acid, the ethyl ester of an essential fatty acid. It is supplied as soft gelatin capsules at 1 g strength for oral administration. The proposed dosing regimen of Vascepa™ is 4 g/day (taken as two capsules twice daily) (b) (4) (b) (4).

A total of 15 clinical studies including 7 clinical pharmacology studies or studies with clinical pharmacology components are submitted in the NDA database. The conducted clinical pharmacology studies meet the regulatory requirements for filing and this application is fileable from a clinical pharmacology perspective. The filing meeting was held on 11/09/2011.

The key clinical trials that contributed to safety and efficacy database in hypertriglyceridemia include a pivotal Phase III trial MARINE (AMR-01-01-0016) and a supportive Phase III trial ANCHOR (AMR-01-01-0017). Additionally, the sponsor is using 8 trials in CNS indications to support safety.

Table 1 lists PK studies in healthy subjects and Table 2 lists studies in hypertriglyceridemic patients with PK measurements.

Table 1: PK Studies in Healthy Volunteers

Study ID	Study Objective	Study Design	Subjects No. (M/F) Age (range or mean in years)	Dose, Dosage Form, Route of Administration [Product Batch ID*]	Sample Type	Analyte	Assay
LA01.01.0009	Safety & PK	Phase 1, single-center, open-label, randomized, single and repeated dose study	Group A 12 M Mean 33 yr	SD of 2 g (four 0.5 g Vascepa capsules) on Day 1 + MD of 2 g/day (four 0.5 g Vascepa capsules QD) on Days 3-30 [212797AR1]	Plasma RBC	Total EPA	GC/FID (in µg/g)
			Group B 12 M Mean 33 yr	SD of 2 g (four 0.5 g Vascepa capsules) on Days 1 and 30 + MD of 2 g/day (four 0.5 g Vascepa capsules QD) on Days 3-29 [212797AR1]	Plasma RBC	Total EPA	
AMR-01-01-0018	PK	Phase 1, single-center, open-label, randomized, repeated dose study	48 Subjects 24 M/24 F, 20 to 55 yr	2 g/day: one 1 g Vascepa capsule BID [256189A]	Plasma Plasma RBC	Total EPA Unesterified EPA Total EPA	LC/MS-MS (in µg/mL)
				4 g/day: two 1 g Vascepa capsules BID [256189A]			
				2 g/day: two 1 g Vascepa capsules QD [256189A]			
				2 g/day: two 0.5 g Vascepa capsules BID [231171A]			
AMR-01-01-0020	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	30 Subjects 19 M/11F 20 to 55 yr	Omeprazole With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Omeprazole	LC/MS-MS
				Rosiglitazone With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Rosiglitazone	LC/MS-MS
AMR-01-01-0021	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	26 Subjects 20 M/6 F 20-55 yr	Warfarin With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	R-warfarin S-warfarin	LC/MS-MS
AMR-01-01-0023	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	30 Subjects 22 M/8 F 20-54 yr	Atorvastatin With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Atorvastatin, 4-hydroxy-atorvastatin, 2 hydroxy-atorvastatin -	LC/MS-MS

HV = healthy volunteers; P = patients; M/F = males/females; EPA = eicosapentaenoic acid; RBC = red blood cells; SD = single dose; MD = multiple dose
* Bulk capsule lot number;
† Plasma samples at a few time points were also analyzed for total and unesterified EPA by LC/MS-MS.

Table 2: Studies in Hypertriglyceridemic Patients with PK Measurements

Study ID	Study Objective	Study Design	Subjects No. (M/F) Age (range years)	Dose, Dosage Form, Route of Administration [Product Batch ID*]	Sample Type	Analyte	Assay
AMR-01-01-0016 (MARINE)	Safety/Efficacy & PK	Phase 3, multi-center, double-blind, placebo-controlled, randomized, repeated-dose	229 Patients (175 M/54 F) 27 to 79 yr	Placebo [XI07A1 and XI07A2]	Plasma RBC	Total EPA	LC/MS-MS (in µg/mL)
				2 g/day: one 1 g Vascepa oral capsule BID [XI07A1, XI07A2, XI07B2, XI07B3]			
				4 g/day: two 1 g Vascepa capsules BID [XI07B2 and XI07B3]			
AMR-01-01-0017 (ANCHOR)	Safety/Efficacy & PK	Phase 3, multi-center, double-blind, placebo-controlled, randomized, repeated-dose	702 Patients (431 M/271 F) 31 to 88 yr	Placebo [XI07A1 and XI07A2]	Plasma RBC	Total EPA	LC/MS-MS (in µg/mL)
				2 g/day: one 1 g Vascepa oral capsule BID [XI07A1, XI07A2, XI07B2, XI07B3]			
				4 g/day: two 1 g Vascepa capsules BID [XI07B2 and XI07B3]			

HV = healthy volunteers; M/F = males/females; EPA = eicosapentaenoic acid; RBC = red blood cells
* Bulk capsule lot number

Studies LA01.01.0009 and AMR-01-01-0018 are two single dose and multiple dose PK studies in healthy subjects. Studies AMR-01-01-0020, AMR-01-01-0021, and AMR-01-01-0023 are three drug-drug interaction studies to evaluate the effect of Vascepa™ on four substrates. Trough plasma levels of total EPA after repeated dose administration of Vascepa™ in patients with hyperlipidemia were examined at daily doses of 2 and 4 g/day in the MARINE and ANCHOR studies in patients with elevated TG levels.

Following single and multiple oral doses of Vascepa™, peak plasma concentrations of EPA were reached approximately 5 hours. Both C_{max} and AUC increased in approximate proportion to the Vascepa dose. In hypertriglyceridemic patients, plasma concentrations of EPA (trough levels) increased by 309% and 678% at steady state after oral administration of Vascepa 2 g/day and 4 g/day, respectively.

The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA

circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is the unesterified fatty acid. Greater than 99% of unesterified EPA in plasma is bound to plasma proteins.

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. The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($T_{1/2}$) of EPA at steady state is approximately 89 hr. Vascepa does not undergo renal excretion.

In studies with healthy adult subjects, co-administration of 4 g/day Vascepa with either omeprazole, rosiglitazone, warfarin or atorvastatin did not affect the AUC or C_{max} of exposure of the tested concomitant medications. In addition, 4 g/day Vascepa did not affect the anticoagulation of warfarin.

Dosing with 2 g/day Vascepa as a QD regimen versus a BID regimen resulted comparable EPA AUC at steady state. Preliminary evaluation from the sponsor showed no gender or age effect on EPA exposure.

Potential key clinical pharmacology review questions include:

- What are the single dose and multiple dose PK of Vascepa in healthy subjects?
- What are the PK comparisons when Vasepa is administered as 2 g/day BID; 2 g/day QD; or 4 g/day BID?
- What is the PK comparison between 0.5 g and 1 g strength capsules?
- Is there a gender or age effect on the PK of Vascepa?
- Is there a dose-response relationship for the percent reduction in fasting TG level from baseline to Week 12 compared to PBO?
- What is the effect of Vascepa on the PK of the concomitant medications in the three DDI studies?

Annotated Label

11 PAGES OF DRAFT LABELING HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) IMMEDIATELY FOLLOWING THIS PAGE

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

/s/

ZHIHONG LI
06/01/2012

IMMO ZADEZENSKY
06/01/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-057	**Reviewer:** Houda Mahayni, Ph.D.	
Submission Date:	September 26, 2011, January 30, 2012, and May 29, 2012		
Division:	DMEP	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Applicant:	Amarin Pharma Inc.		
Trade Name:	Vascepa™	**Date Assigned:**	September 27, 2011, January 31, 2012, and May 29, 2011
Generic Name:	Icosapent Ethyl (AMR101)	**Date of Review:**	March 23, 2012, May 25, 2012, and May 29, 2012
Indication:	Treatment of patients with very high triglycerides (≥ 500 mg/dL)	**Type of Submission:** Original NDA, Response to 74-Day Filing Letter, and Amendment to tighten the disintegration specification	
Formulation/strengths	Capsule/1 g		
Route of Administration	Oral		

SUBMISSION:

The Applicant submitted a 505 (b) (1) NDA for Vascepa™(icosapent ethyl) Capsules, 1 g, referred to as AMR101. The proposed indication is for the treatment of patients with very high triglycerides (≥500 mg/dL).

The Biopharmaceutics review will evaluate the proposed disintegration test and acceptance criterion, the manufacturing site change, the components and compositions change, and the change in batch size (scale-up).

BIOPHARMACEUTIC INFORMATION:

The Proposed Disintegration Test and Acceptance Criterion

At the IND stage (IND 102,457), the Applicant asked FDA to accept a disintegration test in lieu of dissolution test for quality control testing. The Applicant referred to FDA's agreement that a dissolution test for AMR101 capsules is not required. This agreement was provided as a response to the Applicant's CMC meeting request (Correspondence for IND 102,457, reference ID: 2893874, Communication Date 01/20/2011).

The Applicant selected a disintegration test using USP <701> (b) (4)

The Applicant performed a study to justify the selection of the disintegration media. The objective of the study was to determine a suitable media to demonstrate discrimination in disintegration or rupture time. The Applicant exposed AMR101 capsules, 1 g to several stress conditions, as follows:

(b) (4)

Subsequently, the Applicant tested six stressed and unstressed capsules using USP <701> for disintegration time and rupture time using each of the following media:

(b) (4)

The Applicant reported that the media tested showed unremarkable differences in rupture and disintegration times between the stressed capsules and the unstressed capsules. (b) (4) The Applicant stated that historically only disintegration time data (not rupture time) were collected during the development program for AMR101 capsules, 1 g. The Applicant stated that the capsule must rupture prior to disintegrating. Therefore, a specification for disintegration time (rather than rupture time) is considered a more discriminating measure of the performance of AMR101 capsules, 1 g.

Reviewer's Note:
The disintegration time is not an appropriate terminology or description to use for a gelatin capsule, as it ruptures not disintegrates to release its contents. Therefore, the more suitable terminology to use in this case is rupture time.

The Applicant stated that nine batches of AMR101 Capsules, 1 g, were manufactured. These batches are summarized in Table 3 below. The nine batches ranges from (b) (4) capsules, which is approximately (b) (4) of the proposed commercial scale (b) (4) capsules. The batches were manufactured by Banner Pharmacaps Europe and Catalent Pharma Solutions.

Table 3: Summary of AMR101 Capsule, 1 g Batches

Bulk Drug Product Lot Number	Batch Size (capsules)	Place of Manufacture	Date of Manufacture	Drug Substance Batch Number[a]	Use
249353A	(b) (4)	Banner	October 2008	EE020AX	Clinical study 0016 (open label) Supportive stability
249354A		Banner	October 2008	EE070IX	Clinical study 0016 (double blind) Clinical study 0017 (double blind) Supportive stability
249355A		Banner	October 2008	EE100LX	Clinical study 0016 (open label) Clinical study 0017 (double blind) Supportive stability
249356A		Banner	October 2008	EE020AX	Supportive stability
256188A		Banner	March 2010	EE020AX	Primary stability
256189A		Banner	March 2010	EE130FW	Clinical study 0016 (open label) Clinical study 0018 Clinical study 0020 Clinical study 0021 Clinical study 0023 Primary stability
256190A		Banner	March 2010	EE050LY	Primary stability
263672A		Banner	June 2011	EE100LX, EE130FW EE0701X	Process verification (development study)
1204849		Catalent	June 2011	EE020BB	Primary stability

[a] All drug substance batches of icosapent ethyl were supplied by Nisshin Pharma, Inc.

The disintegration results of the above batches are listed in Table 4 below.

Table 4: Batch Analysis Data for Bulk AMR101 Capsules, 1 g

(b) (4)

Table 5 shows the disintegration time obtained from the 12 months and 24 months stability data for the following batches: 256188A, 256189A, 256190A, 249353A, 249356A, 249356A, 249354A, 249355A, 249356A under different storage conditions.

Table 5: Stability Study for AMR101 Capsules, 1 g

(b) (4)

Based on the above information, The Applicant proposed a disintegration specification of NMT (b) (4) for release and shelf-life.

Reviewer's Note:
The proposed disintegration specification is not acceptable, as it is too wide based on the data provided in Table 4 for Lot Release and Table 5 for Shelf-Life.

At the NDA Filing, FDA identified several Biopharmaceutics issues and sent Information Request to the Applicant on 12/08/2011. The Biopharmaceutics issues related to the disintegration method and acceptance criterion are listed below. The Applicant responded to the Information Request on 01/30/2012.

FDA Request:
1. Provide the method development report of the disintegration test including the parameters for the proposed disintegration test: medium, volume, apparatus, time, procedure and tolerances.

Applicant Response:
The disintegration test follows USP <701>. The volume, apparatus, procedure, and tolerances are consistent with the USP <701> monograph. At the Agency's request (please refer to correspondence for IND 102,457, reference ID: 2893874), Amarin performed a study to justify the selection of (b) (4) *the disintegration medium. The study was summarized in Section 3.2.P.2.2.1.3 of the NDA. Section 3.2.R of the NDA has been amended to include the following report: Investigation of Media for the Disintegration of AMR101 Capsules, 1 g.*

Reviewer's Note:
The response is acceptable.

FDA's Request:
2. Submit disintegration results generated on batches used in both clinical and stability studies. The specification will be set after FDA reviews the disintegration results generated from these batches.

Applicant's Response:
Disintegration results for bulk AMR101 Capsules, 1 g, used in clinical and stability studies are provided in Section 3.2.P.5.4 of the NDA. For the reviewer's convenience, these data are reproduced in the table 6 below. In addition, disintegration results for all stability time points are provided in Section 3.2.P.8.3 of the NDA.

Table 6: Summary of Disintegration Data for Bulk AMR101 Capsule, 1 g, Batches

Bulk Drug Product Lot Number	Batch Size (capsules)	Place of Manufacture	Date of Manufacture	Use	Disintegration Results[a] (minutes)
249353A	(b) (4)	Banner	October 2008	Clinical study 0016 (open label) Supportive stability	(b) (4)
249354A		Banner	October 2008	Clinical study 0016 (double blind) Clinical study 0017 (double blind) Supportive stability	
249355A		Banner	October 2008	Clinical study 0016 (open label) Clinical study 0017 (double blind) Supportive stability	
249356A		Banner	October 2008	Supportive stability	
256188A		Banner	March 2010	Primary stability	
256189A		Banner	March 2010	Clinical study 0016 (open label) Clinical study 0018 Clinical study 0020 Clinical study 0021 Clinical study 0023 Primary stability	
256190A		Banner	March 2010	Primary stability	
263672A		Banner	June 2011	Process verification (development study), Clinical study 0019 Stability	
1204849		Catalent	June 2011	Primary stability	
1204850		Catalent	September 2011	Primary stability Clinical study 0019[b]	
1204851		Catalent	September 2011	Primary stability Clinical study 0019[b]	
264010A[c]		Banner	November 2011	Stability[b] Clinical study 0019[b]	
264818A[c]		Banner	November 2011	Stability[b] Clinical study 0019[b]	

[a] Disintegration for bulk AMR101 Capsules, 1 g, using USP <701>

[b] Intended use. The activity has not yet been initiated.

[c] Batches not presented in NDA submission

Reviewer's Note:

The above response is acceptable. For the record, the Applicant provided the above table (Table 6) in the original submission. However, it did not include the disintegration results column. The table provided in the original submission is shown in Table 3 above.

Also, the disintegration specification of NMT (b) (4) is not acceptable. All the clinical and stability batches at the pilot (11 batches) or commercial scale (2 batches) disintegrated in less than (b) (4), as shown in Table 6 above. Therefore, FDA requests that the Applicant change the disintegration specification to NLT (b) (4).

FDA held a teleconference meeting with the Applicant on May 24, 2012 to request tightening the disintegration specification to NMT (b) (4). The Applicant stated that the disintegration results provided in the NDA are obtained from pilot batches (batch size (b) (4) capsules). However, the intended commercial batch size is (b) (4) capsules. The Applicant expressed concern that the commercial batch may not meet the specification of

NMT [redacted]. The Applicant proposed to have two disintegration specifications for its product (release NMT [redacted] and shelf-life NMT [redacted]). FDA requested the Applicant to set the same disintegration specification for lot release and shelf-life. The Applicant stated that there were lots with shelf-life disintegration result o[redacted]. FDA pointed out that it was only one Lot. It was agreed that the product disintegration specification be set to NMT [redacted] and if the Applicant find that the disintegration specification for the commercial lots is not meeting the specification to submit a Prior Approval Supplement and request expedited review to change the disintegration specification. FDA requested the Applicant to amend the NDA with the agreed upon disintegration specification of NMT [redacted]. The Applicant provided the Amendment on May 29, 2012.

Additionally, during the telecon, FDA stated that the appropriate terminology to use with gelatin capsule is rupture time not disintegration time. The Applicant stated that it found disintegration time more discriminating than rupture time and referred to Table 1 and Table 2 above. FDA disagreed as the data provided did not differentiate between control and capsules under stress conditions. The Applicant offered to provide further information to clarify why the terminology of disintegration time and not rupture time was selected.

Manufacturing Site Change and Components and Composition Change

The Applicant stated that two drug product manufacturers were used to produce AMR101 Capsules, 1g: Banner Pharmacaps Europe BV [Banner] and Catalent Pharma Solutions [Catalent]. Both manufacturers produce AMR 101 capsules, 1 g, using the same components and composition, [redacted]

Table 7. Components and Composition of Drug Product Manufactured by Banner

Component	Unit Quantity (mg/capsule)	Function	Reference to Standard
[redacted]			
Icosapent Ethyl[a]	1000	Active	In-House
[redacted]			
Gelatin	[redacted]		USP/NF, Ph.Eur.
[redacted] Sorbitol [redacted]			USP/NF, Ph.Eur.
Glycerin			USP/NF, Ph.Eur.
Purified Water			USP/NF, Ph.Eur.
Maltitol [redacted]			USP/NF, Ph.Eur.
[redacted]			

The composition of AMR 101 capsules, 1 g, manufactured by Catalent is provided in Table 8 below.

Table 8: Components and Composition of Drug Product Manufactured by Catalent

Component	Unit Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Icosapent Ethyl[a]	1000	Active	In-House
(b) (4)			
Gelatin	(b) (4)		USP/NF
(b) (4) Sorbitol (b) (4)			USP/NF
Glycerin			USP/NF
Purified Water			USP/NF, Ph.Eur.
Maltitol (b) (4)			USP/NF
(b) (4)			

The Applicant reported that the same formulation and manufacturing process for AMR101 capsules, 1 g, was used for all clinical and stability studies, and is the same formulation and process intended for commercial marketing.

In the Information Request sent to the Applicant on 12/08/12, the Biopharmaceutics issue related to the site change is listed below, followed by the Applicant response and the reviewer evaluation.

FDA's Request:
Submit comparative disintegration test results comparing batches manufactured at Banner and Catalent and specify the manufacturing site to be used to manufacture the commercial product.

Applicant's Response:
Comparative disintegration test results comparing batches manufactured at Banner and Catalent are provided in Section 3.2.P.5.4 of the NDA. For the reviewer's convenience, these data are reproduced in the response to Question 11 above. In addition, disintegration results for all stability time points are provided in Section 3.2.P.8.3 of the NDA. Both Banner and Catalent are intended as commercial manufacturing sites for AMR101 Capsules, 1 g.

Reviewer's Note:
The above response is acceptable. For the record, the table provided in the referenced section did not provide comparative disintegration results. The reviewer relied on Table 6 which was provided in the response to the Information Request to address the requested information.

Batch Size Change
The pilot scale batch size ranged (b) (4)). The intended commercial scale batch size (b) (4)). The pilot scale and intended commercial scale processes for AMR 101 capsules, 1 g, at Banner are essentially similar except for (b) (4) The Applicant provided Table 9 below comparing the pilot scale and intended commercial batch scale formulas for AMR101 Capsules, 1g.

Table 9: Comparison of Pilot-Scale and Intended Commercial-Scale Batch Formulas for AMR101 Capsules

Component	Pilot-Scale Batches		Intended Commercial-Scale Batch[e]	
	Batch Quantity (kg)	Batch Proportion (% w/w)	Batch Quantity (kg)	Batch Proportion (% w/w)
Total Batch Size	(b) (4)			
(b) (4)				
Icosapent ethyl[a]				
(b) (4)				
Gelatin				
Non-crystallizing Sorbitol (b) (4)				
Glycerin				
Purified Water[b]				
Maltitol (b) (4)				
Total				
Capsule Count (theoretical)				

In the Information Request sent to the Applicant on 12/08/12, the Biopharmaceutics issue related to batch size change is listed below, followed by the Applicant response and the reviewer evaluation.

FDA's Request:
Submit comparative disintegration test results comparing the pilot scale batches and the intended commercial scale batches.

Applicant's Response:
All AMR101 Capsules, 1 g, that were submitted in the NDA were manufactured at pilot scale, and the data are summarized in Section 3.2.P.5.4 of the NDA. In addition, two batches were manufactured in November 2011 at the commercial-scale. For the reviewer's convenience, all disintegration data are presented in Table 6 above, including the two commercial-scale batches.

Reviewer's Note:
The above response is acceptable. For the record, the Applicant did not provide disintegration results for the commercial scale batch in the Original NDA.

Additionally, in the Information Request sent to the Applicant on 12/08/12, the Biopharmaceutics issue related to related to (b) (4) material is listed below, followed by the Applicant response and the reviewer evaluation.

FDA's Request:
Submit information or data to support that the (b) (4) material does not change with time.

Applicant's Response:
AMR101 Capsules, 1 g, are a highly stable drug product. Section 3.2.P.8.1 and Section 3.2.P.8.3 of the NDA present the stability summary and stability data, respectively.
For the reviewer's convenience, the following table is presented to further summarize that the (b) (4) material does not change with time. This table represents data associated with (b) (4) material for the three primary stability batches (stability study protocol BD10-028). Data are presented from the Drug Substance Certificate of Analysis (as applicable), the Packaged Drug Product Initial Timepoint, and the Packaged Drug Product 12 Month Timepoint from the long-term storage condition. Except for (b) (4) there are no observable trends in the stability data and all values are within the proposed shelf-life limits. (b) (4) shows an upward trend. This trend is always within the proposed shelf-life specification, does not lead to secondary oxidation products as evidenced by the lack of trends in (b) (4), and has no impact on the potency of the product. A statistical analysis was performed (b) (4), which showed the 95% confidence interval well within the proposed shelf-life specification at (b) (4) (please refer to Section 3.2.P.8.3 of the NDA for the statistical analysis).

(b) (4)

Reviewer's Note:
The above response is acceptable.

RECOMMENDATION:
This submission is considered a full response to the Information Request letter dated December 8, 2012. The Applicant fulfilled FDA's requests and provided data to support the proposed disintegration test, the manufacturing site change, and the change in batch size (scale-up). Also, the Applicant agreed to revise the disintegration specification to NMT (b) (4) and amended the NDA with the revised disintegration specification on May 29, 2012.

From the Biopharmaceutics viewpoint, NDA 202-057 for Icosapent Ethyl (AMR101) is recommended for APPROVAL.

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

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

cc: *NDA 202-057 DARRTS*

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
05/30/2012

ANGELICA DORANTES
05/30/2012

BIOPHARMACEUTICS FILING REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 202-057 (0000)	**Reviewer:** Houda Mahayni, Ph.D.	
Division:	DMEP		
Applicant:	Amarin Pharma Inc.	**Biopharmaceutics Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	Vascepa™		
Generic Name:	Icosapent Ethyl (AMR101)	**Date Assigned:**	September 27, 2011
Indication:	Treatment of patients with very high triglycerides (≥500 mg/dL)	**Date of Review:**	November 7, 2011
Formulation	Capsule		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission date	CDER Stamp Date	Date of informal/Formal Consult	PDUFA DATE
September 23, 2011	September 26, 2011	September 27, 2011	July 26, 2012
Type of Submission:	Original NDA		
Type of Consult:	Disintegration Test and Specification, Manufacturing Site Change, and Scale-Up (Batch Size)--- **FILING REVIEW**		

REVIEW SUMMARY:

The Applicant submitted a 505 (b) (1) NDA for Vascepa™(icosapent ethyl) Capsules, 1 g, referred to as AMR101 in some studies. The proposed indication is for the treatment of patients with very high triglycerides (≥500 mg/dL). The components and composition of AMR101 capsules, 1 g, is provided in Table 1 below.

Table 1. Components and Composition of Drug Product Manufactured by Banner

Component	Unit Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Icosapent Ethyl[a]	1000	Active	In-House
(b) (4)			
Gelatin			USP/NF, Ph.Eur.
(b) (4) Sorbitol (b) (4)			USP/NF, Ph.Eur.
Glycerin			USP/NF, Ph.Eur.
Purified Water			USP/NF, Ph.Eur.
Maltitol (b) (4)			USP/NF, Ph.Eur.
			(b) (4)
			See Table 2.3.P.1-2
			Ph.Eur.
			USP/NF, Ph.Eur.
			Ph.Eur.
			USP/NF
			(b) (4)

Disintegration Test and Specification:
The Applicant referred to FDA's agreement that a dissolution test for AMR101 capsules is not required. This agreement was provided as a response to the Applicant's CMC meeting request (Correspondence for IND 102,457, reference ID: 2893874, Communication Date 01/20/2011).

In the above referenced communication, the Applicant posed the question below and FDA provided the following response:

Applicant's Question 4. Amarin proposes that, since the drug substance is an oil and therefore insoluble in water, the dissolution test is not necessary and that the disintegration test is adequate for quality control testing. Does the Agency agree with this approach?

FDA Response: Yes. Provide a justification in the NDA for the choice of disintegration medium and the proposed disintegration time (NMT (b) (4)) specification. Also, for a soft gelatin capsule, "disintegration test" should be more appropriately termed as "rupture test" and the specification should indicate "rupture time".

The Applicant stated that only disintegration time data (not rupture time) were collected during the development program for AMR101 Capsules, 1 g. Therefore, FDA requested the Applicant to conduct a disintegration study to compare the capsule rupture time and capsule disintegration time. The disintegration study was performed using USP <701> (b) (4) (b) (4) . The study's objective was to determine a suitable media to demonstrate discrimination in disintegration or rupture time. Six capsules from each stress condition and six unstressed control capsules were tested for disintegration time and rupture time using each of the following media:

(b) (4)

The Applicant concluded that the capsule must rupture prior to disintegrating and selected a specification for disintegration time (rather that rupture time) as a more discriminating measure of the performance of AMR101 Capsules, 1 g, an immediate-release drug product.

The Applicant reported that the proposed specification is NMT (b) (4) for release and shelf-life, and provided the observed ranges for both as follows:

(b) (4)

Different Manufacturing Sites

The Applicant used two drug product manufacturers to produce AMR101 capsules, 1 g: Banner Pharmacaps Europe BV [Banner] and Catalent Pharma Solutions [Catalent]. The Applicant stated that both manufacturers produce AMR101 capsules, 1 g, using the same components and composition, (b) (4) The Applicant reported that the same formulation and manufacturing process for AMR101 Capsules, 1 g, was used for all clinical and stability studies, and is the same formulation and process intended for commercial marketing.

For AMR101 capsules manufactured by Banner, the Applicant provided a table of the components and composition in the NDA (Table 1 above). However, for AMR101 capsules components and composition manufactured by Catalent, the Applicant referenced the DMF.

Scale-Up (Batch-Size)

The pilot-scale and intended commercial-scale processes for AMR101 Capsules, 1 g, at Banner are essentially unchanged except for (b) (4) . A comparison of the batch formulas is provided in Table 4.

Table 4. Comparison of Pilot-Scale and Intended Commercial-Scale Batch Formulas for AMR101 Capsules, 1 g

Component	Pilot-Scale Batches		Intended Commercial-Scale Batch[e]	
	Batch Quantity (kg)	Batch Proportion (% w/w)	Batch Quantity (kg)	Batch Proportion (% w/w)
Total Batch Size	(b) (4)			(b) (4)
Icosapent ethyl[a]	(b) (4)			
Gelatin	(b) (4)			
Sorbitol	(b) (4)			
Glycerin				
Purified Water[b]				
Maltitol	(b) (4)			
Total				
Capsule Count (theoretical)	(b) (4)			
				(b) (4)

RECOMMENDATION:

The ONDQA/biopharmaceutics team reviewed NDA 202-057(0000) for filing purposes. We found this NDA filable from Biopharmaceutics perspective. The Biopharmaceutics review will focus on the evaluation of the proposed disintegration test and specifications, the different manufacturing sites, and the scale-up (batch size).

Comments to be Conveyed to the Applicant:

- Provide the method development report of the disintegration test including the parameters for the proposed disintegration test: Medium, Volume, Apparatus, Time, Procedure and Tolerances.
- Submit disintegration results generated on batches used in both clinical and stability studies. The specification to be set after FDA reviews the disintegration results generated from these batches.
- Submit the components and composition of the drug product manufactured by Catalent.

- Submit comparative disintegration test results comparing batches manufactured at Banner and Catalent and specify the manufacturing site to be used to manufacture the commercial product.
- Submit comparative disintegration test results comparing the pilot scale batches and the intended commercial scale batches
- Submit information or data to support that the (b) (4) material does not change with time.

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

cc: NDA 202-057, KSharma, KJohnson, STran, MHaber

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
11/10/2011

ANGELICA DORANTES
11/10/2011

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**NDA 202057**	**Brand Name**	**Vascepa™**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**ethyl-EPA**
Medical Division	**DMEP**	**Drug Class**	**Omega-3 fatty acid**
OCP Reviewer	**Zhihong Li**	**Indication(s)**	**Severe hypertriglyceridemia**
OCP Team Leader	**Jayabharathi Vaidyanathan**	**Dosage Form**	**Soft gelatin capsule**
Pharmacometrics Reviewer	**TBD**	**Dosing Regimen**	**4 g/day as BID** (b) (4)
Date of Submission	**9/26/2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**5/26/2012**	**Sponsor**	**Amarin Pharmaceuticals Ireland Ltd.**
Medical Division Due Date		**Priority Classification**	**Standard**
PDUFA Due Date	**7/26/2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	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**		**Test Facility Study No. 310873, 311369, 313125**
I. Clinical Pharmacology		**9**		**LA01.01.0009, AMR-01-01-0018, AMR-01-01-0020, AMR-01-01-0021, AMR-01-01-0023, AMR-NC-11-01, OPT-2010-157, AMR-01-01-0016, AMR-01-01-0017**
Mass balance:				
Isozyme characterization:	**X**	**1**		**AMR-NC-11-01**
Blood/plasma ratio:				
Plasma protein binding:	**X**	**1**		**789867**
Pharmacokinetics (e.g., Phase I) -	**X**	**4**		**LA01.01.0009, AMR-01-01-0018, AMR-01-01-0016, AMR-01-01-0017**
Healthy Volunteers-		**2**		**LA01.01.0009, AMR-01-01-0018**
single dose:	**X**	**1**		**LA01.01.0009**
multiple dose:	**X**	**2**		**LA01.01.0009, AMR-01-01-0018**
Patients-				
single dose:				
multiple dose:	**X**	**2**		**AMR-01-01-0016, AMR-01-01-0017**
Dose proportionality -	**X**	**1**		**AMR-01-01-0018**
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	**X**	**1**		**AMR-01-01-0018**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

In-vivo effects of primary drug:	**X**	**3**		**AMR-01-01-0020, AMR-01-01-0021, AMR-01-01-0023**
In-vitro:	**X**	**2**		**AMR-NC-11-01, OPT-2010-157**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:	**X**	**2**		**AMR-01-01-0016, AMR-01-01-0017**
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**2**		**AMR-01-01-0016, AMR-01-01-0017**
Population Analyses -				
Data rich:				
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				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**12**		**LA01.01.0009, AMR-01-01-0018, AMR-01-01-0020, AMR-01-01-0021, AMR-01-01-0023, AMR-NC-11-01, OPT-2010-157, AMR-01-01-0016, AMR-01-01-0017, Test Facility Study No. 310873, 311369, 313125**

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	No formulation change
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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	
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	
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.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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

None.

Zhihong Li, Ph.D.	11/09/2011
Reviewing Clinical Pharmacologist	Date
Jayabharathi Vaidyanathan, Ph.D.	11/09/2011
Team Leader/Supervisor	Date

RECOMMENDATIONS:

- This NDA application is fileable from a clinical pharmacology perspective
- No comments in the 74-day letter
- No DSI inspection needed for Clinical Pharmacology studies

BACKGROUND:

In accordance with 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (21 USC §355) and 21 CFR §314.50, Amarin Pharmaceuticals Ireland Ltd. has submitted this original New Drug Application (NDA 202057) for Vascepa™ as an adjunct to diet to reduce triglyceride (b) (4) levels in patients with very high (≥500 mg/dL) triglycerides.

Vascepa™ (icosapent ethyl) is a highly purified formulation of ethyl eicosapentaenoic acid, the ethyl ester of an essential fatty acid. It is supplied as soft gelatin capsules at 1 g strength for oral administration. The proposed dosing regimen of Vascepa™ is 4 g/day (taken as two capsules twice daily) (b) (4)

A total of 15 clinical studies including 7 clinical pharmacology studies or studies with clinical pharmacology components are submitted in the NDA database. The conducted clinical pharmacology studies meet the regulatory requirements for filing and this application is fileable from a clinical pharmacology perspective. The filing meeting was held on 11/09/2011.

The key clinical trials that contributed to safety and efficacy database in hypertriglyceridemia include a pivotal Phase III trial MARINE (AMR-01-01-0016) and a supportive Phase III trial ANCHOR (AMR-01-01-0017). Additionally, the sponsor is using 8 trials in CNS indications to support safety.

Table 1 lists PK studies in healthy subjects and Table 2 lists studies in hypertriglyceridemic patients with PK measurements.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Table 1: PK Studies in Healthy Volunteers

Study ID	Study Objective	Study Design	Subjects No. (M/F) Age (range or mean in years)	Dose, Dosage Form, Route of Administration [Product Batch ID*]	Sample Type	Analyte	Assay
LA01.01.0009	Safety & PK	Phase 1, single-center, open-label, randomized, single and repeated dose study	Group A 12 M Mean 33 yr	SD of 2 g (four 0.5 g Vascepa capsules) on Day 1 + MD of 2 g/day (four 0.5 g Vascepa capsules QD) on Days 3-30 [212797AR1]	Plasma RBC	Total EPA	GC/FID (in µg/g)
			Group B 12 M Mean 33 yr	SD of 2 g (four 0.5 g Vascepa capsules) on Days 1 and 30 + MD of 2 g/day (four 0.5 g Vascepa capsules QD) on Days 3-29 [212797AR1]	Plasma RBC	Total EPA	
AMR-01-01-0018	PK	Phase 1, single-center, open-label, randomized, repeated dose study	48 Subjects 24 M/24 F, 20 to 55 yr	2 g/day: one 1 g Vascepa capsule BID [256189A]	Plasma Plasma RBC	Total EPA Unesterified EPA Total EPA	LC/MS-MS (in µg/mL)
				4 g/day: two 1 g Vascepa capsules BID [256189A]			
				2 g/day: two 1 g Vascepa capsules QD [256189A]			
				2 g/day: two 0.5 g Vascepa capsules BID [231171A]			
AMR-01-01-0020	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	30 Subjects 19 M/11F 20 to 55 yr	Omeprazole With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Omeprazole	LC/MS-MS
				Rosiglitazone With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Rosiglitazone	LC/MS-MS
AMR-01-01-0021	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	26 Subjects 20 M/6 F 20-55 yr	Warfarin With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	R-warfarin S-warfarin	LC/MS-MS
AMR-01-01-0023	Drug Interaction Study (PK) †	Phase 1, single-center, open-label, crossover	30 Subjects 22 M/8 F 20-54 yr	Atorvastatin With/without 4 g/day: two 1 g Vascepa capsules BID [256189A]	Plasma	Atorvastatin, 4-hydroxy-atorvastatin, 2 hydroxy-atorvastatin -	LC/MS-MS

HV = healthy volunteers; P = patients; M/F = males/females; EPA = eicosapentaenoic acid; RBC = red blood cells; SD = single dose; MD = multiple dose
* Bulk capsule lot number;
† Plasma samples at a few time points were also analyzed for total and unesterified EPA by LC/MS-MS.

Table 2: Studies in Hypertriglyceridemic Patients with PK Measurements

Study ID	Study Objective	Study Design	Subjects No. (M/F) Age (range years)	Dose, Dosage Form, Route of Administration [Product Batch ID*]	Sample Type	Analyte	Assay
AMR-01-01-0016 (MARINE)	Safety/Efficacy & PK	Phase 3, multi-center, double-blind, placebo-controlled, randomized, repeated-dose	229 Patients (175 M/54 F) 27 to 79 yr	Placebo [XI07A1 and XI07A2]	Plasma RBC	Total EPA	LC/MS-MS (in µg/mL)
				2 g/day: one 1 g Vascepa oral capsule BID [XI07A1, XI07A2, XI07B2, XI07B3]			
				4 g/day: two 1 g Vascepa capsules BID [XI07B2 and XI07B3]			
AMR-01-01-0017 (ANCHOR)	Safety/Efficacy & PK	Phase 3, multi-center, double-blind, placebo-controlled, randomized, repeated-dose	702 Patients (431 M/271 F) 31 to 88 yr	Placebo [XI07A1 and XI07A2]	Plasma RBC	Total EPA	LC/MS-MS (in µg/mL)
				2 g/day: one 1 g Vascepa oral capsule BID [XI07A1, XI07A2, XI07B2, XI07B3]			
				4 g/day: two 1 g Vascepa capsules BID [XI07B2 and XI07B3]			

HV = healthy volunteers; M/F = males/females; EPA = eicosapentaenoic acid; RBC = red blood cells
* Bulk capsule lot number

Studies LA01.01.0009 and AMR-01-01-0018 are two single dose and multiple dose PK studies in healthy subjects. Studies AMR-01-01-0020, AMR-01-01-0021, and AMR-01-01-0023 are three drug-drug interaction studies to evaluate the effect of Vascepa™ on four substrates. Trough plasma levels of total EPA after repeated dose administration of Vascepa™ in patients with hyperlipidemia were examined at daily doses of 2 and 4 g/day in the MARINE and ANCHOR studies in patients with elevated TG levels.

Following single and multiple oral doses of Vascepa™, peak plasma concentrations of EPA were reached approximately 5 hours. Both C_{max} and AUC increased in approximate proportion to the

Vascepa dose. In hypertriglyceridemic patients, plasma concentrations of EPA (trough levels) increased by 309% and 678% at steady state after oral administration of Vascepa 2 g/day and 4 g/day, respectively.

The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is the unesterified fatty acid. Greater than 99% of unesterified EPA in plasma is bound to plasma proteins.

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. The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life (T1/2) of EPA at steady state is approximately 89 hr. Vascepa does not undergo renal excretion.

In studies with healthy adult subjects, co-administration of 4 g/day Vascepa with either omeprazole, rosiglitazone, warfarin or atorvastatin did not affect the AUC or C_{max} of exposure of the tested concomitant medications. In addition, 4 g/day Vascepa did not affect the anticoagulation of warfarin.

Dosing with 2 g/day Vascepa as a QD regimen versus a BID regimen resulted comparable EPA AUC at steady state. Preliminary evaluation from the sponsor showed no gender or age effect on EPA exposure.

Potential key clinical pharmacology review questions include:

- What are the single dose and multiple dose PK of Vascepa in healthy subjects?
- What are the PK comparisons when Vasepa is administered as 2 g/day BID; 2 g/day QD; or 4 g/day BID?
- What is the PK comparison between 0.5 g and 1 g strength capsules?
- Is there a gender or age effect on the PK of Vascepa?
- Is there a dose-response relationship for the percent reduction in fasting TG level from baseline to Week 12 compared to PBO?
- What is the effect of Vascepa on the PK of the concomitant medications in the three DDI studies?

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/s/

ZHIHONG LI
11/10/2011

JAYABHARATHI VAIDYANATHAN
11/10/2011